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(54) Title: 71 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

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71 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human

growth hormone, tissue plasminogen activator, and erythropoeitin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing

to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein , a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an

overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications.. Polypeptides may be branched , for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,

gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PFCSGFFPSLWIYLPFIFNVSDLWMGSLSGCALPFCLXVFFLTVSPSAVGLLXF
AGGPLQTLFAWVSPVEAAEQQRLLPVLSSGSFVSEGTCQMPARALLYEVSVG

PYWEIPPSQDTRRSGTYLRRQSDP (SEQ ID NO: 195) . Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in pancreas islet cell tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the pancreas, including cancer and diabetes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pancreas, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of pancreatic islet cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment and intervention of such tumors, in addition to other endocrine or gastrointestinal tumors where expression has been indicated. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1099 of SEQ ID NO:11, b is an integer of 15 to 1113, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
HEGSCRAPGFSAHKGRGCPSPRMTLPSRALASLGVGVWGMLRLNQVTVSCG
GSRWSSRVALGAFSWVCGVALVLQPSGGGLGLTSPSEGCWEGELALAVLRA
PGGSPS (SEQ ID NO: 196) . Polynucleotides encoding these polypeptides are also provided.

This gene is expressed equally in in .

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders, particularly leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hemolymphoid, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 104 as residues: Gly-29 to Ser-35, Ser-63 to Cys-68. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in hemangiopericytoma, breast lymph node, and bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO:12, b is an

integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with the Drosophila melanogaster slit protein, a secreted protein that contains both an EGF domain and Leucine Rich Repeat domains. It is thought to be important in the development of midline glia and commissural axon pathways (See e.g., Rothberg et al. Genes Dev. 4:2169-87 (1990); which is hereby incorporated by reference herein).

This gene is expressed primarily in human hippocampus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neurological, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution within human hippocampus combined with the homology to the Drosophila slit protein, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,

Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 959 of SEQ ID NO:13, b is an integer of 15 to 973, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

IPLTLPGIFLLIRLFWRLGQSICGPGKLVLWPQFCCGCAVISGHCVPRGMPSSW
LPGCFVLLCLVAVGCQLREWGVGGVSAVGLLALPHLQVLGMRGRGLISGG
(SEQ ID NO: 197) . Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

This gene is expressed in KMH2 cells, osteoblasts, fetal spleen, Jurkat membrane bound polysomes, breast, and cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, immune, and skeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, skeletal, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in KMH2 cells, osteoblasts, and fetal spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal spleen and T-cells indicates a role in the regulation of the proliferation: survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved

in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1444 of SEQ ID NO:14, b is an

integer of 15 to 1458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with phospholipase A2 which cleaves fatty acids from carbon 2 of glycerol (ref. Prosite pattern documentation for PS2_HIS). Many snake venoms contain phospolipase A2, which prevents transmission of nerve impulses to muscles by blocking the release of acetylcholine from the neuron. Therefore, included in this invention as preferred domains are Phospholipase A2 histidine active site domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). Phospholipase A2 is an enzyme which releases fatty acids from the second carbon group of glycerol. Structurally, PA2's are small and rigid proteins of 120 amino-acid residues that have four to seven disulfide bonds. PA2 binds a calcium ion which is required for activity. The side chains of two conserved residues, a histidine and an aspartic acid, participate in a 'catalytic network'. Two different signature patterns for PA2's were developed. The first is centered on the active site histidine and contains three cysteines involved in disulfide bonds. The consensus pattern is as follows: C-C-x(2)-H-x(2)-C [H is the active site residue].

Preferred polypeptides of the invention comprise a Phospholipase A2 histidine active site domain selected from the following amino acid sequences: CCNQHDRC (SEQ ID NO: 199), SLTKCCNQHDRCYET (SEQ ID NO: 200) , and/or LTKCCNQHDRCYETCG (SEQ ID NO: 201) . Polynucleotides encoding these polypeptides are also provided. Further preferred are polypeptides comprising the Phospholipase A2 histidine active site domain of the sequence listed in Table 1 for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is N-terminal or C- terminal to the Phospholipase A2 histidine active site domain. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the Phospholipase A2 histidine active site domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The

above preferred polypeptide domain is characteristic of a signature specific to Phospholipase A2 proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with Phospholipase A2 proteins. Such activities are known in the art, some of which are described elsewhere herein, or see, for example, McIntosh, et al. J. Biol. Chem. 270 (8), 3518-3526 (1995), incorporated herein by reference.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
GPAGKEAWIWSWLLPSPGPAPLPSASWGLCGDAPR
AAARGPVEPGAARMALLSRPALTLLLLLMAAVVRCQEQAQTTDWRATLKTI
RNGVHKIDTYLNAALDLLGGEDGLCQYKCSDGSKPFPRYGYKPSPPNGCGSP
LFGXHLNIGIPSLTKCCNQHDRCYETCGKSKNDCDEEFQYCLSKICRDVQKTL
GLTQHVQACETTVELLFDSVIHLGCKPYLDSQRAACRCHYEEKTDL (SEQ ID NO: 198) . Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed in a variety of cell types with no single type predominating.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, or metabolism disorders, specifically phospholipase A2 deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuromuscular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pancreas, cancerous and wounded tissues) or bodily fluids (e.g., bile. lymph,

serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 107 as residues: Gln-23 to Asp-30, Lys-66 to Cys-87. Polynucleotides encoding said polypeptides are also provided.

The ubiquitous tissue distribution and homology to phospholipase A2 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuromuscular disorders. Alternatively, considering the activity of phospholipase A2 as a block for neuro- transmission may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, the homology to Phospholipase A2 proteins may indicate a potential use for the protein product of this gene in diagnosis, treatment and/or prevention of metabolism disorders, specifically deficiencies in Phospholipase A2. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1991 of SEQ ID NO:15, b is an integer of 15 to 2005, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

In a specific enbodiment polypeptides of the invention comprise the following amino acid sequence:
GTSSARPRGALPGGSAPSAPHGQLPGRAQPAPVSGPPPTSGLCHFDPAAPWPL
WPGPWQLPPHPQDWPAHPDIPQDWVSFLRSFGQLTLCPRNGTVTGKWRGSH
VVGLLTTLNFGDGPDRNKTRTFQATVLGSQMGLKGSSAGQLVLITARVTTER
TAGTCLYFSAVPGILPSSQPPISCSEEGAGNATLSPRMGEECVSVWSHEGLVLT
KLLTSEELALCGSRLLVLGSFLLLFCGLLCCVTAMCFHPRRESHWSRTRL
(SEQ ID NO: 202) . Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
ARAPPGPEGLSPEAQPPLLPMGNCQAGHNLHLCLAHHPPLVCATLILLLLGLS
GLGLGSFLLTHRTGLRT LTSPRTGSLF (SEQ ID NO: 203). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed in a wide variety of tissue types including testes, cerebellum, dendritic cells, breast cancer, umbilical vein endothelial cells, epididymus, corpus colosum, chronic synovitis, liver hepatome, normal breast, osteoblasts, melanocytes, B cell lymphomas, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, cancer, particularly of endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endothelial, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 108 as residues: Thr-52 to Gly-57. Polynucleotides encoding said polypeptides are also provided.

Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that the protein product of this gene may play a role in the regulation of cellular division and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also relies on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have

applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 929 of SEQ ID NO:16, b is an integer of 15 to 943, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

RFLSVXPQXEVPFLLHPCVCFXGGHPSLLPDPCRAVGGGWEAPRCCLHEALC QSLGCKAEEIVSVSESSSAQRCWYLLRGRKAGGRGPASPVLFALMRLESLCH LCLACLFFRLPATRTVYCMNEAEIVDVALGILIESRKQXKACEQPALAGADNP EHSPPCSVSPHTSSGSSSEEEDSGKQALXPGLSPSQRPGGSSSACSRSPEEEE EEDVLKYVREIFFS (SEQ ID NO: 204) . Polynucleotides encoding these polypeptides are also provided. Polynucleotides of the invention do not consist of the nucleic acid sequences shown as GeneSeq Accession Nos: V59595 and V59744, which are hereby incorporated herein by reference.

This gene is expressed primarily in a variety of immune cell types, including stromal cells, dendritic cells, leukocytes, activated T-cells, macrophages, monoctyes, neutrophils and to a lesser extent in a variety of other adult and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal tissue and various hematopoietic cancers indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all

hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1489 of SEQ ID NO:17, b is an

integer of 15 to 1503, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the NF-kB (Nuclear Factor kB) pathway. Thus, it is likely that this gene activates T-cells through the NF-kB signal transduction pathway. NF-kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity. Preferred polypeptides of the invention comprise the following amino acid sequence: VPGWPRACSPCQADSPRAHPPKLRGILRWAPVPLXCAALCPPLDSG MSMAACPEAPEPSFLREVPSSPASTQWHRPCNFRQVEANPRKEPKNLVWRD VSLGQXSRTPRGSGLELVRVCGGGMQRDKTVVEERVGEERERERERESLGG AGKHGEMRCVYVRESVGAPGRAGGGGNGVNSVGCVRTVHSGSXPPPSAGV S (SEQ ID NO: 205) . Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in parts of the brain such as cerebellum and frontal lobe.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in cerebellum and frontal lobe indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, prevention and/or treatment of neurodegenerative disease states and behavioural disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1498 of SEQ ID NO:18, b is an

integer of 15 to 1512, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
TRPGKELNLVFGLQLSMARIGSTVNMNLMGWLYSKIEALLGSAGHTTLGITL
MIGGITCILSLICALALAYLDQRAERILHKEQGKTGEVIKLTDVKDFSLPLWLIF
IICVCYYVAVFPFIGLGKVFFTEKFGFSSQAASAINSVVYVISAPMSPVFGLLV
DKTGKNIIWVLCA (SEQ ID NO: 206) . Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in fetal tissue, and to a lesser extent in a variety of adult human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fetal abnormalities, particularly developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 111 as residues: Lys-30 to Thr-35. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Furthermore, the protein

may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1641 of SEQ ID NO:19, b is an integer of 15 to 1655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The translation product of this gene shares sequence homology with human histiocyte-secreted factor (HSF) which is a novel cytokine that shows in vivo antitumour activity without the cytotoxicity associated with tumour necrosis factor. Furthermore, The translation product of this gene also shares sequence homology with the human endogenous virus S71 gag polyprotein, the sequence of which is believed to represent a transformation locus for several cancers (See Genebank Accession No. pir|A46312|A46312; all references available through this accession are hereby incorporated by reference herein). Similarly, The translation product of this gene also shares homology with B219, a sequence that is expressed in at least four isoforms in very primitive hematopoietic cell populations which may represent a novel hemopoietin receptor (See, e.g., Cioffi, et al. Nat. Med. 2:585-589 (1996), which is hereby incorporated by reference herein). In a preferred embodiment polypeptides of the invention comprise the following amino acid sequence:

CKDLCSRVYLLTLSPLLSYDPATSHSPRNTQ (SEQ ID NO: 207) . Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in tonsil, and colon, and to a lesser extent in a wide variety of human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and gastrointestinal disorders, particularly tumors of the colon and tonsil. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic, digestive and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, gastrointestinal, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 112 as residues: Met-1 to Cys-6. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tonsil and colon, combined with the homology to human histiocyte growth factor, the human endogenous viral protein, and B219 strongly indicate that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment and/or prevention, of a variety of hematopoietic and immune system disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation

of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2511 of SEQ ID NO:20, b is an

integer of 15 to 2525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
IICECWEEECQSCRLKITQPREICRMDFLVLFLFYLASVLMGLVLICVCSKTHS
LKGLARGGAQIFSCIIPECLQRAXHGLLHYLFHTRNHTFIVLHLVLQGMVYTE
YTWEVFGYCQELELSLHYLLLPYLLLGVNLFFFTLTCGTNPGIITKANELLFLH
VYEFDEVMFPKNVRCSTCDLRKPARSKHCSVCNWCVHRFDHHCVWVNNCI
GAWNIRYFLIYVLTLTASAATVAIVSTTFLVHLVVMSDLYQETYIDDLGHLHV
MDTVFLIQYLFLTFPRIVFMLGFVVVLSFLLGGYLLFVLYLAATNQTTNEWYR
GDWAWCQRCPLVAWPPSAEPQVHRNIHSHGLRSNLQEIFLPAFPCHERKKQE
(SEQ ID NO: 208) . Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in colon and brain and to some extent in all tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and digestive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neurological, gastrointestinal, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternatively, expression of this gene in colon may indicate a role in the detection, prevention and/or treatment of colon diorders such as colon cancer, Crohn's Disease, ulcers, and digestive tract disorders in general. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1382 of SEQ ID NO:21, b is an integer of 15 to 1396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

When tested against Reh cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates B-cells through the Jaks-STAT signal transduction pathway. GAS isa promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. This gene maps to chromosome 7, and therefore, is used as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in brain, and in the developing embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, behavioral, immune, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and developmental systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developing, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue

or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 114 as residues: Lys-60 to Asn-67. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the tissue distribution in developing embryo indicates that the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, the biological activity within B-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Activation of genes witin B-cells indicates a role for this protein in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1055 of SEQ ID NO:22, b is an integer of 15 to 1069, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

LLSFKIRGLRTEDAGWAQSSSGGLCVRGDAFWMPSSSSGLGSPSRPPSSFLCL
LLLLLPPAALALLLFFLDFFPPRAAVSPFLPDHCSARQPRVWRRETLNRSASGL

GCWARSTEQGAVGVATGTVLDI SLPASCLSLWPPGPSGGI (SEQ ID NO: 209) . Polynucleotides encoding these polypeptides are also provided.

In a specific embodiment polypeptides of the invention comprise the following amino acid sequence: QLGLCLTSASLPPASRCGHQAPLGASDLSAHHSAPGFSDSYFTMSCQSSLSRA EILQCPLVPSVSPPTHLPQGRANKSSRASLPLLPQTHWCLFPSARGWRRGIQSG LPPGGSCTSPRSPPQTLHQHITLVNHNTSYWQSPST (SEQ ID NO: 210) , HQPPCLLPLAVATRPLWGHLTCLPIILHLVSVTLTSPCLANQAFQGQRSYNAL WCPLFLLLPTSPKGEQTNHPEPACPCFPKLTGVFSLQHVVGAEEFSQVFLLVD PVPVLDHLLKLFTSTSHLLIIIPHIGKAPAPDSLL EELSLSLATHCKVAVARFT (SEQ ID NO: 211) . Also preferred are the polynucleotides encoding these polypeptides. Polynucleotides of the invention do not consist of the nucleic acid sequence shown as GeneSeq Accession No. X04377, which is hereby incorporated herein by reference.

This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, behavioral and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 115 as residues: Pro-2 to Gly-7, Ser-10 to Ser-16,

Pro-52 to Val-62, Arg-64 to Ser-73. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1644 of SEQ ID NO:23, b is an

integer of 15 to 1658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

The translation product of this gene was shown to have homology to the lysosomal mannosidase alpha-B protein (See Genebank Accession No. P34098) which is thought to be important in protein metabolism. One embodiment of this gene comprises polypeptides of the following amino acid sequence:
MAAEGSRFSSQSPGLVDRQGPKCDPSRLVSPWGRHGLRILQIGHHHGRDGQH
EATHHLLRVLRAPRVGKADEGAVDSDPSTPLQLKHEAAHAEDHAQQVHVVR
RRVVQGRVTFARRGLVPQHFVRPPWVRHIVSGHSESKARSRLFRCRNRSFRR
AS (SEQ ID NO: 212) , and/or
RLVSPWGRHGLRILQIGHHHGRDGQHEATHHLL RVLRA (SEQ ID NO: 213) .
An additional embodiment is the polynucleotides encoding these polypeptides. This gene maps to chromosome 19, and therefore, is used as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in brain, placenta, fetal liver, and to a lesser extent in most tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, reproductive, and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hepatic, or cancerous and wounded tissues) or bodily fluids (e.g., bile, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 116 as residues: Asn-34 to Lys-42, Leu-60 to Trp-70. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution predominantly in brain indicates a role in the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntinton's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Alternatively, the tissue distribution in liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1063 of SEQ ID NO:24, b is an integer of 15 to 1077, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

This gene is expressed primarily in spinal cord, Merkel cells, and adipose tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorders of the nervous and immune systems, particularly those disorders relating to the CNS involving lipid metabolism disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and immune systems and adipose tissue, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spinal cord, Merkel cells and adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases the nervous systems, such as spinal cord injury, neurodegenerative diseases, muscular dystrophy or obesity. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1191 of SEQ ID NO:25, b is an integer of 15 to 1205, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with the human uncoupling protein-2 which is thought to be important in energy metabolism, obesity, and the predisposition of hyperinsulinemia (See Genebank Accesion No. gi|1857278). Recently, another group published on this gene, designating it brain mitochondrial carrier protein-1 (BCMP1) (J Biol Chem 1998 Dec 18;273(51):34611-5). One embodiment of this gene comprises polypeptides of the following amino acid sequence: PTDVLKIRMQAQ (SEQ ID NO: 214) , and/or TYEQLKR (SEQ ID NO: 215) . An additional embodiment is the polynucleotides encoding these polypeptides. This gene maps to the X chromosome, and therefore, is used as a marker in linkage analysis for the X chromosome.

This gene is expressed primarily in manic depression brain tissue, epileptic frontal cortex, human erythroleukemia cell line, T-helper cells, and to a lesser extent in endothelial and amygdala cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system or hematopoietic/immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system or hematopoietic/immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hemolymphoid, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 118 as residues: Ser-34 to Thr-39, Gln-198 to Leu-205. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neural tissues combined with the homology to the human uncoupling protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Alternatively, given the homology to uncoupling proteins, the gene and/or its translation product may also be used in the diagnosis, treatment, and/or prevention of thermogenesis disorders such as obesity, cachexia, and hyperinsulinemia. Uncoupling proteins dissipate the proton gradient created from the oxidation of fuels by the electron transport chain, thus releasing stored energy as heat. Dysfunction of thermogenesis can induce disorders such as obesity and cachexia. It is thought that obesity may result from decreased thermogenesis in humans. Alternatively, cachexia is a metabolic state in which energy expenditure exceeds food intake, for example in anorexia nervosa. Uncoupling proteins is useful for the treatment and/or prevention of diseases and/or disorders involved with aberrant metabolic and thermogenic pathways. The following method provides for the determination of respiration uncoupling activity of the polypeptides of the present invention, including fragments and variants of the full length proteins.

Briefly, yeast are transfected with an expression vector expressing polypeptide of the present invention as previously described by Bouillaud et al., EMBO J., 13:1990 (1994) (incorporated by reference herein in its entirety). Rates of growth in liquid medium of transformed yeast are measured in the presence of galactose, which induces expression, as described in International Publication No. WO 98/31396

(incorporated by reference herein in its entirety). Instantaneous generation times are compared between the polypeptide of the present invention and appropriate controls. An in vivo decrease of membrane potential associated with uncoupling of respiration is analyzed by flow cytometry of yeast labeled with the potential sensitive probe DiOC6 (3) (3,3'-dihexyloxacarbocyanine iodine, Molecular Probes, Eugene, OR). The ability of a polypeptide of the present invention to influence mitochondrial activity and uncouple respiration is thus determined.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:26, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene shares sequence homology with 55 kD deglycosylated zona pellucida protein which is known to be important in egg fertilization (See Genebank Accession No.R39356). Preferred polypeptides of the invention comprise the following amino acid sequence:
RPRPSASSLARSASLLPAAHGXGVGGAGGGSSXLRSRYQQLQNEEESGEPEQ AAGDAPPPYSSISAESAHXFDYKDESGFPKPPSYNVATTLPSYDEAERTKAEA TIPLVPGRDEDFVGRDDFDDADQLRIGNDGIF (SEQ ID NO: 216), RYQQLQNEEESGEPEQAAGD (SEQ ID NO: 217), and/or PGRDEDFVGRDDFDDADQLRIG (SEQ ID NO: 218). Polynucleotides encoding these polypeptides are also provided.

Preferred polypeptide fragments of the invention comprise the following amino acid sequence: MLTFFMAFLFNWIGFFLSFCLTTSAAGRYG AISGFGLSLIKWILIVRFSTYFPGYFDGQY WLWWVFLVLGFLLFLRGFINYAKVRKMPET FSNLPRTRVLFIY (SEQ ID NO: 219). Polynucleotides encoding these polypeptides are also provided.

Preferred polypeptide varients of the invention comprise the following amino acid sequence: MKKSLENLNRLQVMLLHLTAAFLQRAQHXFDYKDESGFPKPPSYNVATTLPS YDEAERTKAEATIPLVPGRDEDFVGRDDFDDADQLRIGNDGIFMLTFFMAFLF NWIGFFLSFCLTTSAAGRYGAISGFGLSLIKWILIVRFSTYFPGYFDGQYWLW WVFLVLGFLLFLRGFINYAKVR KMPETFSNLPRTRVLFIY (SEQ ID NO: 220), MLLHLTAAFLQRAQFSTYFPGYFDGQYWLWWVFLVLGFLLFLRGFINYAKV RKMPETFSN LPRTRVLFIY (SEQ ID NO: 221), MLTFFMAFLFNWIGFFLSFCLT TSAAGRYGAISGFGLSLIKWILIVRFSTYFPAFMNSLSRSKRTPAGSESRCRTQ RNNHLL (SEQ ID NO: 222), and/or MKKSLENLNRLQVMLLHLTAAFLQRAHXIL TTRMSLGFQSPHLTM (SEQ ID NO: 223). Polynucleotides encoding these polypeptides are also provided.

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in adult kidney, colon adenocarcinoma, and fetal brain, and to a lesser extent, ubiquitously expression in many tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorders of kidney, colon cancers, and central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal and neural systems, and cancers, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., renal, neural, urogenital, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 119 as residues: Cys-15 to Gly-36. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution adult kidney, colon adenocarcinoma, and fetal brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of kidney diseases, colon cancers, and disorders of the central nervous system. Additionally, the homology to the zona pellucida protein indicates that the gene product is used for male contraceptive development, and infertility diagnosis etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1951 of SEQ ID NO:27, b is an

integer of 15 to 1965, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

The translation product of this gene shares sequence homology with the chicken transferrin receptor in addition to a human prostate-specific protein homolog (See Genebank Accession Nos.pir|JH0570|JH0570 and gi|2565338 (AF026380), respectively). This gene also shares significant homology with both the murine and the rat hematopoietic lineage switch 2 proteins (See Genbank Accession Nos. g3169729 and g3851632, respectively), which are induced during an erythroid to myeloid lineage switch.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MTVMDPKQMNVAAAVWAVVSYVVADMEEML PRS (SEQ ID NO: 224). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in fetal tissues, such as liver/spleen and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pre-natal disorders, anomalies, deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 120 as residues: Arg-31 to Lys-37, Lys-58 to Glu-65,

Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of pre-natal disorders, anomalies and deficiencies. The homology to the hematopoietic lineage switch 2 proteins indicates that The translation product of this gene is useful for the detection and/or treatment of immune system disorders. In addition, the homology to the transferrin receptor indicates that the translation product of the present invention may have utility in the regulation of iron metabolism as well as the numerous genes under the stringent control of physiologic iron levels. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1849 of SEQ ID NO:28, b is an integer of 15 to 1863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRSREPVAGAPGCGTAGPPAMATLWGGLLRLGSLLSLSCLALSVLLLAHC
QTPPSDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLL
LYMVYLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANV

LNKVEYAQQRWKLQVQEQRKSVFDRHVVLS (SEQ ID NO: 225). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 72 - 88 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 89 to 167 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

A preferred polypeptide varient of the invention comprise the following amino acid sequence:
MATLWGGLLRLGSLLSLSCLALSVLLLAHCQTPPRISRMSDVNVSALPIKKNS
GHIYNKNISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIII
YLSILGLLLLYMVYLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLA
RSRSRANVLNKVEYGTAALEASSPRAAKSLSLTGMLSSANWGIEFKVTRKKQ
ADNWKGTDWVLLGFILIPC (SEQ ID NO: 226). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in infant brain tissue, and to a lesser extent in other cell types and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system, such as depression, schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, mania, dementia, paranoia, addictive behavior, sleep disorders, epilepsy, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developmental, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic

fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 121 as residues: Gln-110 to Pro-120, Val-152 to Val-159. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of developmental, degenerative and behavioral conditions of the brain and nervous system. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), mania, depression, dementia, paranoia, addictive behavior, obsessive-compulsisve disorder and sleep disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1612 of SEQ ID NO:29, b is an

integer of 15 to 1626, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

The translation product of this gene shares sequence homology with a recently published gene Dysferlin, which is thought to be a skeletal muscle gene that is mutated in Miyoshi myopathy and limb girdle muscular dystrophy (See Genbank Accession No. g3600028, and Nat. Genet. 20 (1), 31-36 (1998)).

This gene is expressed primarily in fetal liver, fetal heart tissue, and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, tumor necrosis, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and liver disorders, vascular disorders, and cancers (e.g., hepatoblastoma, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, developmental, vascular, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-supressive conditions (transplantation) and hematopoeitic disorders. In addition this gene product is applicable in conditions of general

microbial infection, inflammation or cancer. Expression in liver may suggest a role for this gene product in the treatment and detection of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Alternatively, the tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stoke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the homology to the dysferlin gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diseases related to degenerative myopathies that are characterized by the weakness and atrophy of muscles without neural degradation; such as Duchenne and Becker's muscular dystropies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:30, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in haemopoietic cells and tumor cells, such as pancreatic tumor tissue, and to a lesser extent in bladder cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic disorders, diseases of the renal and pancreatic systems, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic, pancreatic, and renal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pancreas, renal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the renal, pancreatic and haemopoietic systems, and cancers thereof. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 917 of SEQ ID NO:31, b is an integer of 15 to 931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in liver tissue, cancer cells and fetal lung tissue, and to a lesser extent in dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, diseases of developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus, metabolic systems and cancers, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, metabolic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 124 as residues: His-44 to Gly-49. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the fetus, metabolic systems and cancers. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1393 of SEQ ID NO:32, b is an integer of 15 to 1407, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

This gene is expressed primarily in central nervous system tissues and cancers, such as endometrial tumors, and to a lesser extent in other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the CNS and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and cancerous tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 125 as residues: Tyr-16 to Ser-22, Asp-209 to Leu-215. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in endometrial tumors. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1512 of SEQ ID NO:33, b is an integer of 15 to 1526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

The translation product of this gene shares sequence homology with low-density lipoprotein receptor (See Genbank Accession No. >dbj|BAA24580.1), which is thought to be important in the pathogenesis of atherosclerosis and other disorders.

The translation product of this gene also shares sequence homology with a rat homolog of the human CD94 (See Genbank Accession No. gb|AAC10220.1).

This gene is expressed primarily in macrophages, eosinophils, neutrophil and other cells of the haemopoietic and immune system.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune and haemopoietic systems and diseases of the endothelial and vascular system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, haemopoietic and vascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 126 as residues: Lys-9 to Ala-17, Met-55 to Leu-61, Tyr-105 to Cys-127, Asp-132 to Lys-141, Ser-165 to Tyr-172, Pro-178 to Met-186, His-222 to Gln-227. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to LDL receptor and rat CD94 homolog indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the immune, haemopoietic and vascular systems. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoieitic lineages. Expression of this gene product in eosinophils and macrophage also strongly indicates a role for this protein in immune

function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1723 of SEQ ID NO:34, b is an integer of 15 to 1737, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

A preferred polypeptide fragment of the invention comprises the following amino acid sequence:
MAAAGRLPSSWALFSPLLAGLALLGVGPVPARALHNVTAELFGAEAWGTLA
AFGDLNSDKQTDLFVLRERNDLIVFLADQNAPYFKPKVKVSFKNHSALITSVV
PGDYDGDSQMDVLLTYLPKNYAKSELGAVIFWGQNQTLDPNNMTILNRTFQ
DEPLIMDFNGDLIPDIFGITNESNQPQILLGGNLSWHPALTTTSKMRIPHSHAFI
DLTEDFTADLFLTTLNATTSTFQFEIWENLDGNFSVSTILEKPQNMMVVGQSA
FADFDGDGHMDHLLPGCEDKNCQKSTIYLVRSGMKQWVPVLQDFSNKGTL
WGFVPFVDEQQPTEIPIPITLHIGDYNMDGYPDALVILKNTSGSNQQAFLLENV
PCNNASCEEARRMFKVYWELTDLNQIKDAMVATFFDIYEDGILDIVVLSKGY
TKNDFAIHTLKNNFEADAYFVKVIVLSGLCS NDCPRR (SEQ ID NO: 227).
Polynucleotides encoding these polypeptides are also provided.

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the JAK-STAT

signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in infant brain and placental tissues, and to a lesser extent in several other tissues including cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain disorders and diseases of developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and fetal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 127 as residues: Leu-56 to Thr-62, Gln-80 to Pro-87, Gly-106 to Gln-113, Pro-122 to Lys-127, Gln-138 to Asn-146. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neural tissues and developing tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the central nervous system, disorders of developing systems, and cancers. The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful

for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product is produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product is produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2228 of SEQ ID NO:35, b is an integer of 15 to 2242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

Preferred polypeptides of the invention comprise the following amino acid sequence:
MTKREDGGYTFTATPEDFPKKHKAPVIDIGIANTGKFIMTASSDTTVLIWSLK
GQVLSTINTNQMNNTHAAVSPCGRFVASCGFTPDVKVWEVCFGKKGEFQEV
VRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWKLWDTXVEYKKKQDPY
LLKTGRFEEAAGAXPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH
GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGHLKRASNEST
RQRLQQQLTQAQETLKSLGALKK (SEQ ID NO: 228). Polynucleotides encoding such polypeptides are also provided.

The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Recently, another group published this gene, naming it WS beta-transducin repeats protein (See Human Genetics 103 (5), 590-599 (1998); which is hereby incorporated herein by reference), in which it was suggested that the protein is involved in William's Disease.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 12 - 28 of the amino acid sequence referenced in

Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
VIRHEGSTNMELSQMSXLMGLSVLLGLLALMATAAVXRGWLRAGEERSGRP
ACQKANGFPPDKSSGSKKQKQYQRIRKEKPQQHNFTHRLLAAALKSHSGNIS
CMDFSSNGKYLATCADDRTIRIWSTKDFLQREHRSMRANVELDHATLVRFSP
DCRAFIVWLANGDTLRVFKMTKREDGGYTFTATPEDFPKKHKAPVIDIGIAN
TGK
FIMTASSDTTVLIWSLKGQVLSTINTNQMNNTHAAVSPCGRFVASCGFTPDVK
VWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWK
LWDTXVEYKKKQDPYLLKTGRFEEAAGAXPCRLALSPNAQVLALASGSSIHL
YNTRRGEKEECFERVHGECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAM
VEEMQGHLKRASNESTRQRLQQQLTQAQETLKSLGALKK (SEQ ID NO: 229).
Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in testes, synovial sarcoma and fetal tissues, and to a lesser extent in several other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the reproductive and developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, seminal fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes tissue, synovial sarcoma, and fetal tissues, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the reproductive and developing systems, and cancers. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. This protein is useful for

the treatment, detection, and/or prevention of William's Disease. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2221 of SEQ ID NO:36, b is an integer of 15 to 2235, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

Preferred polypeptides of the invention comprise the following amino acid sequence positions 1-363, 2-363, 4-363, 5-363, 30-363, 31-363, 32-363, 75-363, 76-363 and 82-363 of the following amino acid sequence: MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTL FFAFECRYLAVQLSPAIPVFAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIE MEIEATNGAVPQGQRPPPRIKNFQINNQIVKLKYCYTCKIFRPPRASHCSICDN CVERFDHHCPWVGNCVGKRNYRYFYLFILSLSLLTIYVFAFNIVYVALKSLKI GFLETLKETPGTVLEVLICFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTG KNRVQNPYSHGNIVKNCCEVLCGPLPPSVLDRRGILPLEESGSRPPSTQETSSS LLPQSPAPTEL NSNEMPEDSSTPEEMPPPEPPEPPQEAAEAEK (SEQ ID NO: 230). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide varient of the invention comprises the following amino acid sequence: MLFLFSMATLLRTSFSDPGVIPRALPDEAA

FIEMEIEATNGAVPQGQRPPPRIKNFQINNQIVKLKYCYTCKIFRPPRASHCSIC DNCVE RFDHHCPWVGNCVGKRNYRYFYLFILSLSLLTIYVFAFNIVYVALK SLKIGFLETLKGNS WNCSRSPHLLLYTLVRRGTDWISYFPRGSQ PDNQ (SEQ ID NO: 231). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in ovarian and endometrial tumors, fetal liver, spleen and brain tissues, and to a lesser extent in several other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the developing systems, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing, female reproductive and fetal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 129 as residues: Pro-44 to Lys-54, Cys-88 to His-95, Val-103 to Tyr-108, Gln-181 to Ser-190, Thr-192 to Ile-206, Glu-233 to Ser-245, Ser-252 to Ala-286. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in developing systems indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of developing and fetal systems, and cancers. Furthermore, the tissue distribution in ovarian and endometrial tumor tissues indicates that the translation product of this gene is useful for the detection, diagnosis, and/or treatment of cancers of the female reproductive system. Accordingly, preferred are antibodies

which specifically bind a portion of The translation product of this gene. Also provided is a kit for detecting these tumors. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2957 of SEQ ID NO:37, b is an integer of 15 to 2971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in normal and cancerous colon tissue, macrophages, endothelial cells and placental tissue, and to a lesser extent in several other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and gastrointestinal disorders, immune disorders, vascular diseases and disorders of developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune , vascular and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, gastrointestinal, developmental, vascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 130 as residues: Thr-27 to Ser-33. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in macrophage, endothelial and placental tissues, and normal and cancerous colon tissues, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of immune, gastrointestinal and vascular disorders and diseases. Expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting colon cancer. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting colon cancer in an individual which comprises a step of contacting an antibody specific for The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Alternatively, the tissue distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders

of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product is produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta and endothelial cells also indicates that this gene product is produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Additionally, expression of this gene product in macrophage also strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1149 of SEQ ID NO:38, b is an integer of 15 to 1163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The translation product of this gene shares homology with HNK-sulfotransferase, which directs glycan synthesis (see Genbank Accession no. AF033827).

This gene is expressed primarily in activated T cells, osteoclastoma, and glioblastoma, and to a lesser extent in various other normal and transformed cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, immune defects, cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hemopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 131 as residues: Pro-32 to Gly-48, Gln-63 to Thr-69, Pro-77 to Trp-84, Val-88 to Leu-94. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in T-cells and various types of neoplasms indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, study and/or treatment of inflammatory and general immune defects, and various types of neoplasms. Expression of this gene product in T cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in various cancerous tissues indicates that the translation product of the gene is useful for the detection, diagnosis, and/or treatment of these cancers, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1918 of SEQ ID NO:39, b is an integer of 15 to 1932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

Preferred polypeptides of the invention comprise the following amino acid sequence:
LHECLPGSISYLHPRTPWLCLPPQHLSFSTFSPPWQPAMSPVPGTGGPPCGL (SEQ ID NO: 232), and/or
MLPLLIICLLPAIEGKNCLRCWPELSALIDYDLQILWVTPGPPTELSQSIHSLFLE
DNNFLKPWYLDRDHLEEETAKFFTQVHQAIKTLRDDKTVLLEEIYTHKNLFT
ERLNKISDGLKEKGAPPLHECLPGSISYLHPRTPWLCLPPQHLSFSTFSPPWQP
AMSPVPGTGGPPCGL (SEQ ID NO: 233). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in infant brain, testes and activated T cells, and to a lesser extent in various other normal and transformed cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, reproductive and inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural, immune and male reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 132 as residues: Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Ala-123. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in infant brain tissue, testes tissue, and activated T-cells, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis, and/or treatment of neurological, reproductive and immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell type. Alternatively, the tissue distribution in testes tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Furthermore, the tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 867 of SEQ ID NO:40, b is an integer of 15 to 881, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares sequence homology with some human and rodent melanoma and leukocyte specific antigens (see, for example, Genbank accession nos: gi|189384, gi|205898 and gi|180926). In addition, The translation product of this gene shares sequence homology with Tetraspan protein (see, for example, Genbank accession number: GI 3152703). Therefore, it is likely that the polypeptide of this gene shares some biological functions, such as cell-to-cell signaling, adhesion, proliferation, and differentiation with Tetraspan.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 52-68 and 197 - 213 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed

that the protein product of this gene shares structural features to type IIIa membrane proteins.

The transmembrane 4 superfamily (TM4SF) or tetraspan superfamily has at least 16 members (including CD9, CD20, CD37, CD53, CD63, CD81, CD82, A15, CO-029, Sm23, RDS, Uro B, Uro A, SAS, Rom-1, PETA3, and YKK8), is the second biggest subfamily among CD antigen superfamily. and activation antigen of T- cells. All TM4SF member contains four putative transmembrane domains, two extracellular loops, and two short cytoplasmic tails. They are variously expressed on Immature, early, mature, activated lymphocytes, monocytes, macrophages, granulocytes, platelets, eosinophils, basophils, certain leukemic and lymphoma cells, and a variety of other cells and tissues. CD9 cell surface protein is expressed by both hematopoietic and neural cells, and may play a role for CD9 in intercellular signaling in the immune and nervous system. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule, which play important role in cell adhesion of platelets and endothelial cells. Increased mRNA for CD63 antigen was found in atherosclerotic lesions of Watanabe heritable hyperlipidemic rabbits, suggesting a potential role of CD63 in progression of atherosclerosis. CD63 is also a mast cell marker.

CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be a target for the development of a drug for this leukemia. CD81 is the target of an antiproliferative antibody. A diverse group of human cell lines, including hematolymphoid, neuroectodermal, and mesenchymal cells, express the CD81 protein. Many of the lymphoid cell lines, in particular those derived from large cell lymphomas, were susceptible to the antiproliferative effects of the antibody. CD81 may therefore play an important role in the regulation of lymphoma cell growth. CD9, CD20, CD37, CD63, CD81 and CD82 have been implicated in the regulation of cell growth, adhesion, and signal transduction of B, T lymphocytes and some other non-lymphoid cells. They associate with CD2, CD21, CD4, CD8, MHC Class II molecules, integrins, function as co-receptor for T, B and other lymphoid cells. Some

TM4SF are leukocyte antigens, highly expressed in activated leukocytes, lymphocytes, are highly specific surface marker for lymphoblastic leukemia, lymphoma, melanoma, and neuroblastoma. CD9 has been show to be involved in cell motility and tumor metastasis. These antigen could be a valuable immunogen or target to implement active and passive immunotherapy in patients with cancer. Others have been shown to be involved in inhibition of prostate cancer metastasis. This gene has close homology to C33 antigen (CD82). whic is a member of the transmembrane 4 superfamily (TMSF) and activation antigen of T- cells. C33 Ag (CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be very important target for developing drug for leukemia. Other members of this family are Sm23, CO-029, R2, TAPA-1, CD9, CD37, CD53, and CD63. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule.

There is strong evidence indicating that CD63 and Pltgp40, a platelet membrane glycoprotein are the same molecule and that CD63/Pltgp40 is identical to the well-characterized, stage-specific melanoma-associated antigen ME491. These antigen could be valuable immunogens or target to implement active and passive immunotherapy in patients with cancer.

This gene is expressed primarily in fetal tissue (kidney, heart, liver, spleen, brain), macrophages, dendritic cells, retina and to a lesser extent in various other tissues, mostly of lymphoid origin or epithelial cell types. In addition This gene is expressed in cancerous tissues (e.g. breast).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders and cancers in a variety of organs and cell types. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, proliferating, immune, hematopoietic, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid, spinal fluid, or amniotic fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 133 as residues: Tyr-123 to Tyr-131, Cys-134 to Ser-145, Tyr-234 to Tyr-244. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution fetal cells and tissues and homology to tumor antigens indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of lymphoid and epithelial disorders and neoplasms. Additionally, tissue distribution in immune cells and other tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoesis, including cancers. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity

disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1918 of SEQ ID NO:41, b is an integer of 15 to 1932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene shares limited sequence homology with VEGF which is thought to be important in regulation of endothelial cell growth. Therefore, it is likely that the protein encoded by this gene would share some similar biological functions.

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, nervous system disease and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 134 as residues: Thr-25 to Pro-46. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1150 of SEQ ID NO:42, b is an integer of 15 to 1164, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The translation product of this gene shares sequence homology with human p150 which is thought to be important in signal transduction in neuronal cells. Therefore, it is likely that the protein encoded by this polynucleotide would share some similar biological functions with p150.

This gene is expressed primarily in whole embryo and cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and growth defects/disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, expression of this gene

at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of central nervous system, neurodevelopmental, cognitive, and memory disorders. The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked

by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1091 of SEQ ID NO:43, b is an integer of 15 to 1105, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in PMA stimulated HL-60 cells and to a lesser extent in 6 week embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting cell differentiation, particulary hematopoietic disorders and/or defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 136 as residues: Pro-61 to Asp-68. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study of cellular differentiation and for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. The tissue distribution also

indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types Aditionally, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue

differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:44, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and/or defects of the digestive tract including but not limited to cancers of the gastrointestinal tract. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at

significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the digestive system particulary disorders involving the colon. Further, expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the colon and/or other gastrointestinal tissue including, but not limited to, stomach, small intestine, large intestine, and rectum.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 503 of SEQ ID NO:45, b is an integer of 15 to 517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene is expressed primarily in blood cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, immune and hematopoietic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 138 as residues: Pro-19 to Cys-29, Thr-35 to Glu-44, Val-72 to Lys-78. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis and/or treatment of disorders of the immune and hematopoietic system. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 844 of SEQ ID NO:46, b is an

integer of 15 to 858, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed in multiple tissue systems such as brain, immune cells, prostate, uterus, testes, placenta, and fetal heart as well as in cancerous tissues such as ovarian tumors. .

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune, reproductive, urogenital, and central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous sytem and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, reproductive, urogenital, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 139 as residues: Tyr-33 to Lys-38. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, urogenital, reproductive, and central nervous systems. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors. The tissue

distribution in central nervous system tissues also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. . Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in

proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution in uterus indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelyhood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote heathy development of the endometrium. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed

against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6093 of SEQ ID NO:47, b is an integer of 15 to 6107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene is expressed in a wide range of tissue systems such as brain, immune cells, fetal liver, kidney, testes, breast, and pancreas as well as cancerous tissue such as ovarian tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system, immune system, urogenital, and reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, CNS, urogenital, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 140 as residues: Met-1 to Ser-7, Asp-32 to Pro-43, Ser-96 to Arg-102. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, reproductive, urogenital and central nervous systems. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue

differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 689 of SEQ ID NO:48, b is an integer of 15 to 703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in macrophages and fetal cells and to a lesser extent in cancerous ovarian tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases, disorders of developing tissues, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of developmental abnormalities and disorders of the immune systems. The tissue distribution cancerous ovaries indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Expression of this gene product in macrophage cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation.

The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders such as melanomas.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 625 of SEQ ID NO:49, b is an integer of 15 to 639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

This gene is expressed primarily in neutrophils, bone marrow, brain, and fetal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders, Limbic system disfunction/defects and disorders of the immune system and developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, Limbic system and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 142 as residues: Ala-84 to Gln-93. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, Limbic system, CNS and developing systems. Expression of this gene product in bone marrow, eosinophils, and neutrophils strongly indicates a role for this protein in hematopoiesis and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune

Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury.

Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the

"Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 853 of SEQ ID NO:50, b is an

integer of 15 to 867, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

This gene is expressed primarily in ovary and to a lesser extent in fetal tissue, colon, and immune cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, gastrointestinal and immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, gastrointestinal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 143 as residues: Ile-23 to Ala-29. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer and related metastases. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The tissue distribution in colon tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the gastrointestinal tract. This may include diseases associated with digestion and food absorption, as well as hematopoietic disorders involving the

Peyer's patches of the small intestine, or other hematopoietic cells and tissues within the body. Similarly, expression of this gene product in colon tissue indicates again involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1555 of SEQ ID NO:51, b is an integer of 15 to 1569, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase pseudogene. In addition, this gene shares homology with human interferon-beta (Genseq accession number T35524; all references available through this accession are hereby incorporated herein by reference), therefore, it is likely that this gene and the protein encoded by this gene shares some similar biological functions with this protein.

This gene is expressed primarily in frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily

fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in frontal cortex and homology to retrovirus-related reverse transcriptase pseudogene and human interferon-beta indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative diseases of the brain, particularly of the frontal cortex. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, multiple schlerosis, cystic fibrosis, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:52, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene is expressed primarily in immune cells, brain, fetal tissue, and cancerous tissues (such as testes, stomach, lung, pancreas, ovaries) and to a lesser extent in other numerous tissues including, but not limited to, testes and kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and immune cells expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 145 as residues: Lys-23 to Lys-35, Met-46 to Tyr-52. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative disorders of the frontal cortex, as well as, cancer or a number of tissues including but not limited to testes, stomach, lung, pancreas, and ovaries. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 931 of SEQ ID NO:53, b is an integer of 15 to 945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

This gene is expressed primarily in epithelioid sarcoma and to a lesser extent in pancreatic carcinoma, aorta endothelial cells induced with TNF-alpha, and amniotic cells induced with TNF. This gene is also expressed, to a lesser extent, in cancerous lung and ovary tissue and fetal tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, epithelioid sarcoma and related cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., amniotic, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 146 as residues: Tyr-39 to Arg-51. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of certain cancers, including epithelioid sarcoma and pancreatic carcinoma. The tissue distribution in tumors of lung, ovary, and pancreas origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of

developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including

blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 474 of SEQ ID NO:54, b is an

integer of 15 to 488, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
PPVPPWISLPLTGSPPRPGFVPVSPFCFSPMTNGHQVLLLLLLTSAVAAGPWPQ
VHAGQWGWMCLPPGLPSVQARSGLGGLPGGPQWVPGGARGY (SEQ ID NO: 234). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in fetal and infant tissue, particularly infant brain and fetal liver/spleen libraries, and to a lesser extent in breast, ovary tumor, pharynx carcinoma, endometrial stromal cells, thymus, islet cell tumors, and adult cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and breast, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, developmental, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in developing cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis

and treatment of cancer and other proliferative disorders. The expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2846 of SEQ ID NO:55, b is an integer of 15 to 2860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
IQQWGDSVLGRRCRDLLLQLYLQRPELRVPVPEVLLHSEGAASSSVCKLDGLIHRFITLLADTSDSRALENRGADASMACRKLAVAHPLLLLRHLPMIAALLHGRTHLNFQEFRQQNHLSCFLHVLGLLELLQPHVFRSEHQGALWDCLLSFIRLLLNYRKSSRHLAAFINKFVQFIHKYITYNAPAAISFLQKHADPLHDLSFDNSDLVMLKSLLAGLSLPSRDDRTDRGLDEEGEEESSAGSLPLVSVSLFTPLTAAEMAPYMKRLSRGQTVEDLLEVLSDIDEMSRRRPEILSFFSTNLQRLMSSAEECCRNLAFSLALRSMQNSPSIAAAFLPTFMYCLGSQDFEVVQTALRNLPEYALLCQEHAAVLLHRAFLVGMYGQMDPSAQISEALRILHMEAVM (SEQ ID NO: 235).
Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in breast cancer, and to a lesser extent in a variety of other cancers, including uterine cancer, synovial sarcoma, and pharynx carcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer; proliferative diseases and/or disroders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For

a number of disorders of the above tissues or cells, particularly of the breast, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, breast, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, breast milk, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 148 as residues: Glu-35 to His-41, Ser-62 to Ala-67, Pro-145 to Leu-155, Glu-157 to Ser-163, Arg-190 to Val-197, Asp-208 to Pro-215, Ser-247 to Pro-252. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in breast cancer tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of cancer. Elevated expression of this gene product in cancers, such as breast cancer, suggest that it is involved in the abnormal proliferation of cells, dedifferentiation, angiogenesis, and other processes that accompany the development of cancer. Thus, therapeutics targeted against this gene product is useful therapeutic products in and of themselves. Alternately, expression of this gene product at elevated levels in breast tissue is reflective of expression within breast lymph nodes, and may suggest a hematopoietic role for this protein. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1545 of SEQ ID NO:56, b is an integer of 15 to 1559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares limited sequence homology with cytochrome-c oxidase. An alternative embodiment is the polypeptide comprising the following amino acid sequence:
MLLKHLQRMVSVPQVKASALKVVTLTANDKTSVSFSSLPGQGVIYNVIVWD
PFLNTSAAYIPAHTYACSFEAGEGSCASLGRVSSKVFFTLFALLGFFICFFGHR
FWKTELFFIGFIIMGFFFYILITRLTPIKYDVNLILTAVTGSVGGMFLVAVWWR

FGILSICMLCVGLVLGFLISSVTFFTPLGNLKIFHDDGVFWVTFSCIAILIPVVF MGCLRILNILTCGVIGSYSVVLAIDSYWSTSLSYITLNVLKRALNKDFHRAFTN VPFQTNDFIILAVWGMLAVSGITLQIRRERGRPFFPPHPYKLWKQERERRVTNI LDPSYHIPPLRERLYGRLTQIKGLFQKEQPAGERTPLLL (SEQ ID NO: 236).

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: WARLRGPGAHARTSPQPWRGPSPAQAAMGFLQLLVVXVLXSEHRVAGAAE VFGNSSEGLIEFSVGKFRYF ELNRPFPEEAILHDISSNVTFLIFQIHSQYQNTTVSFSPRRRSPTM (SEQ ID NO: 237). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in keratinocytes, brain, and spinal cord and to a lesser extent in hematopoietic cells and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; hematopoietic disorders; integumentary disroders; immune dysfunction; learning disabilities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., integumentary, neural, developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and spinal cord cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

diagnosis and treatment of a variety of neurological and hematopoietic disorders. For example, elevated levels of expression of this gene product in brain and spinal cord indicates that it is involved in neurodegenerative disorders. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternately, expression of this gene product in hematopoietic cells indicates that it is involved in the proliferation, differentiation, survival, and activation of all hematopoietic lineages, including stem and progenitor cells. Expression of this gene product in keratinocytes indicates that it is involved in normal skin function, and could be involved in skin disorders, dermatitis, and fibrosis. The protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e.wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, uticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox,

molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, althletes foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chrondomalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, amd chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2050 of SEQ ID NO:57, b is an integer of 15 to 2064, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRPASPPVRSPARWGSMAGSPLLWGPRAGGVGLLVLLLLGLFRPPPALCA
RPVKEPRGLSAASPPLARLALLAASGGQCPEVRRRGRCRPGAGAGASAGAER

QERARAEAQRLRISRRASWRSCCASGAPPATLIRLWAWTTTPTRLQRSSLALCSAPALTLPP (SEQ ID NO: 238). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in human pituitary and to a lesser extent in pineal gland, and other areas of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pituitary dysfunction; abnormal growth; neurological defects; insufficient milk secretion; abnormal smooth muscle contraction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, breast milk, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 150 as residues: Pro-36 to Gly-42, Pro-64 to Ala-76, Gly-83 to Ala-90, Ser-100 to Cys-108, Thr-126 to Ser-135. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution primarily in pituitary cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders. Elevated expression of this gene product in the pituitary indicates that it is possibly a hormone-like substance that either controls pituitary development itself, or various processes controlled by the pituitary. These include growth, milk secretion, smooth muscle contraction, diuresis, blood pressure, and homeostasis. Thus, this gene product may have numerous clinical

applications. Expression of this gene product in other regions of the brain also indicates that it is involved in normal neurological function, and is useful in the treatment of a variety of neurological disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancrease (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-,hypoparathyroidism) , hypothallamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1036 of SEQ ID NO:58, b is an integer of 15 to 1050, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRLATPNIWDLSMLFAFISLLVMLPTWWIVSSWLVWGVILFVYLVIRALRL

WRTAKLQVTLKKYSVHLEDMATNSRAFTNLVRKALRLIQETEVISRGFTLVS AACPFNKAGQHPSQHLIGLRKAVYRTLRANFQAARLATLYMLKNYPLNSES DNVTNYICVVPFKELGLGLSEEQISEEEAHNFTDGFSLPALKVLFQLWVAQSS EFFRRLALLLSTANSPPGPLLTPALLPHRILSDVTQGLPHAHSACLEELKRSYE FYRYFETQHQSVPQCLSKTQQKSRELNNVHTAVRSLQLHLKALLNEVIILEDE LEKLVCTKETQELVSEAYPILEQKLKLIQPHVQASNNCWEEAISQVDKLLRRN TDKKGKPEIACENPHCTVSTFEAAYSTHCRQRSNPRGAGIRSLCR (SEQ ID NO: 239). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 7 - 23 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 24 to 390 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in prostate and placenta and to a lesser extent in pancreatic tumors and hematopoietic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer; pancreatic cancer; prostate dysfunction; hematopoietic disorders; reproductive diseases and/or disorders, and pancreatitis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, prostate, pancease, placental, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 151 as residues: Pro-85 to Ser-94, Pro-127 to Thr-136, Glu-154 to Glu-160, Phe-240 to Ser-250, Leu-255 to Leu-265, Leu-341 to Lys-351, Thr-372 to Gly-384. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate and placental cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of reproductive disorders. Elevated expression of this gene product in the prostate indicates that it is involved in normal prostate function, and is a diagnostic marker for prostate cancer. Alternately, expression of this gene product in placenta indicates that it may play a role in normal vascular function, and is involved in such processes as angiogenesis and endothelial cell chemotaxis. Thus, this gene product is useful in the treatment of myocardial infarction, cancer, ischemia, and diabetic retinopathy. Expression of this gene product in placenta may also be indicative of fetal health and development.

Similarly, expression of this gene product in hematopoietic cells indicates that it is involved in the proliferation, differentiation, survival, or activation of all hematopoietic cell lineages. Finally, expression of this gene product in pancreatic cancers indicates that it may play a role in cancer in general, or in pancreatic function. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases

and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2519 of SEQ ID NO:59, b is an integer of 15 to 2533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

When tested against Jurkat and K562 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) and ISRE (interferon-sensitive responsive element) promoter elements, respectively. Thus, it is likely that this gene activates myeloid, leukemia, and to a lesser extent, other immune or hematopoietic cells and tissue cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. ISRE is also a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: AAPHPPLLRPLCLWCPLWPAWPLRGRPRSAWKRWPPLPVGPAKLGCSMTTR QPTAVSWPCWLMSSSLSTACLAWTLTGSLAREATRRARSLSPTWNCSARQV PPSPPHSGLGRRGWAHCHLT CLLVTQLFRVGRIHPILSLPLVT (SEQ ID NO: 240). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular diseases; aberrant angiogenesis; neurological disorders; learning disorders; placental insufficiency; and fetal distress. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and neurological systems (CNS/PNS), expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, reproductive, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 152 as residues: Met-1 to Thr-7, Glu-36 to Ser-43, Pro-46 to Gly-63. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain and placental cells and tissues, combined with the detected GAS and ISRE biological activties, indicates that the protein products of this gene are useful for the diagnosis and/or treatment of a variety of neural, reproductive, and vascular diseases and/or disorders. neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Expression of this gene product in placenta indicates that it may play a role in blood vessel development or function, as the placenta is a highly vascularized organ. Thus, this gene product is involved in such processes as angiogenesis, endothelial cell chemotaxis, and vascular cord formation. Thus, it is useful in the treatment of such conditions as myocardial infarction; ischemia; and cancer. Alternately, expression of this gene product in the brain indicates that it may play a role in the survival, proliferation, or function of neurons, and thus is useful in the diagnosis and treatment of such neurological disorders as ALS, schizophrenia, and

Alzheimer's Disease. It may likewise be involved in learning disorders as well. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 885 of SEQ ID NO:60, b is an integer of 15 to 899, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: LQLASQSAGIKGMSHCARPTFLTLLLASCFWAAAIPNRNVILSVSFRPLHMQFTLSILVFILRILILLRSFL (SEQ ID NO: 241). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 40 - 56 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 57 to 60 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in spleen derived from patients with chronic lymphocytic leukemia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic lymphocytic leukemia; hematopoietic disorders; impaired immune function; cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of hematopoietic disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Elevated expression of this protein in the spleens of patients with CLL indicates that it is a useful marker for thi's Disease. Alternately, it is associated with the development and/or progression of the disease, and is a useful target for therapeutic intervention. Additionally, this gene

product may play more general roles in hematopoiesis, and may serve to control cellular decisions regarding proliferation, survival, activation, and/or differentiation of all hematopoietic cell lineages. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1065 of SEQ ID NO:61, b is an integer of 15 to 1079, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

The translation product of this gene shares sequence homology with a putative tyrosine protein kinase from the Chilo iridescent virus. See, for example, Genbank accession no. gi|2738451 (AF003534). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with tyrosine kinase and signaling proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed in a variety of tissues, including microvascular endothelial cells, dendritic cells, and fetal tissues. as well as several tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, vascular, immune, and developmental diseases and/or disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, immune, developmental, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 154 as residues: Ala-21 to Lys-31, Arg-41 to Cys-56, Thr-92 to Cys-102, Arg-132 to Val-137, Lys-152 to Ile-159, Pro-199 to Ser-205, Arg-210 to Asp-219, Ser-225 to Lys-230, Tyr-236 to Ala-241, Lys-243 to Leu-249, Thr-375 to Asp-381. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to a tyrosine kinase indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1914 of SEQ ID NO:62, b is an

integer of 15 to 1928, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 155 as residues: Gly-63 to Ser-72. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker for neutrophil monitoring in cancer and/or immune suppressed patients and/or during chemotherapy or radiation therapy. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and

elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 767 of SEQ ID NO:63, b is an integer of 15 to 781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

This gene is expressed primarily in IL-1 and LPS induced neutrophils, and to a lesser extent, in fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and neural diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 156 as residues: Ile-28 to Trp-37, Ser-68 to Lys-81. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker in neutrophils to monitor patients who are immune suppressed or cancer patients during chemotherapy or radiation therapy. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in

regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1180 of SEQ ID NO:64, b is an integer of 15 to 1194, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

This gene is expressed primarily in prostate.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, urogenital diseases and/or disorders, particularly prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., urogenital, prostate, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 157 as residues: Arg-30 to Gln-36. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate cancer cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of prostate cancer and other urogenital disorders. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis,

treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1663 of SEQ ID NO:65, b is an integer of 15 to 1677, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

A preferred polypeptide of the invention comprises the following amino acid sequence:
MVLVLRHPLCARERAFREPGRGLLTRTGQHDGAPAVTAVPGPLGAVAAAEG RRSAWGAGGSSPPRKVLWGDMRGRRAGVDVLGPALSSEAAGAEARGWGM PGMGVGVGASETRGALFLGREGVHGPCPMDGLGPWPWGPW (SEQ ID NO: 242). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in rejected kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., urogenital, renal, kidney, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 158 as residues: Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in kidney indicates the protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritus, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. The protein is useful for modulating the immune response to aberrant proteins, as may exist in proliferating cells and tissues. Such modulation of the immune response would also show utility in inhibiting the rejection of transplanted tissues, particularly of the renal system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1223 of SEQ ID NO:66, b is an integer of 15 to 1237, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

The translation product of this gene shares sequence homology with both human and mouse Fibulin-2 which is an extracellular matrix protein found in heart tissue (See Genbank Accession Nos. emb|CAA57876.1 and emb|CAA53040.1, respectively; all references available through these accessions are hereby incorporated

herein by reference; for example, J. Cell Biol. 123 (5), 1269-1277 (1993)). Preferred polypeptides encoded by this gene comprise the following amino acid sequence: MGPAVKMWTNAWKGLDDCHYNQLCENTPGGHRCSCPRGYRMQGPSLPCL DVNECLQLPKACAYQCHNLQGSYRCLCPPGQTLLRDGKACTSLERNGQNVT TVSHRGPLLPWLRPWASIPGTSYHAWVSLRPGPMALSSVGRAWCPPGFIRQN GVCTDLDECRVRNLCQHACRNTEGSYQCLCPAGYRLLPSGKNCQDINECEEE SIECGPGQMCFNTRGSYQCVDTPCPATYRQGPSPGTCFRRCSQDCGTGGPSTL QYRLLPLPLGVRAHHDVARLTAFSEVGVPANRTELSMLEPDPRSPFALRPLRA GLGAVYTRRALTRAGLYRLTVRAAAPRHQSVFVLLIAVSPYPY (SEQ ID NO: 243). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MRVLVVTIAPIYWALARESGEALNGHSLTGGKFRQSHTWSLLQGAAHDDPV ARGLDPDGLLLLDVVVNGVVPGRAWLTQIFKCRTLKKHYVQTRAWPAVRG LHTALLPGRPPLVPTLQPQHPVQRGPGPPAPAGAAPAGLSYQLGL (SEQ ID NO: 244). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: HASGAFLVVRGEPQGSWGSMTGVINGRKFGVATLNTSVMQEAHSGVSSIHSS IRHVPANVGPLMRVLVVTIAPIYWALARESGEALNGHSLTGGKFRQESHVEF ATGELLTMTQWPGVWIPMASCSSTWWSMALSPDSLADADLQVQDFEEHYV QTGPGQLFVGSTQRFFQGGLPSFLRCNHSIQYNAARGPQPQLVQHLRASAISS AFDPEAEALRFQLATALQAEENEVGCPEGFELDSQGAFCVDVDECAWDAHL CREGQRCVNLLGSYRCLPDCGPGFRVADGAGCEDVDECLEGLDDCHYNQLC ENTPGGHRCSCPRGYRMQGPSLPCLDVNECLQLPKACAYQCHNLQGSYRCL CPPGQTLLRDGKACTSLERNGQNVTTVSHRGPLLPWLRPWASIPGTSYHAWV SLRPGPMALSSVGRAWCPPGFIRQNGVCTDLDECRVRNLCQHACRNTEGSY QCLCPAGYRLLPSGKNCQDINECEEESIECGPGQMCFNTRGSYQCVDTPCPAT YRQGPSPGTCFRRCSQDCGTGGPSTLQYRLLPLPLGVRAHHDVARLTAFSEV

GVPANRTELSMLEPDPRSPFALRPLRAGLGAVYTRRALTRAGLYRLTVRAAA PRHQSVFVLLIAVSPYPY (SEQ ID NO: 245). Polynucleotides encoding these polypeptides are also provided.

When tested against U937 and Jurkat cell lines, supernatants removed from cells containing this gene repeatedly activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid, T-cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the kidney and renal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., renal, urogenital, kidney, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 159 as residues: Lys-32 to Ser-37, His-89 to Gly-94, Asn-124 to Gln-130, Ala-163 to Val-168, Cys-196 to Arg-201, Gln-244 to Gln-264,

His-288 to Tyr-294, Leu-314 to Gln-319, Ala-392 to Ser-399, Pro-412 to Asp-419, Ala-452 to Pro-460, Arg-466 to Thr-473. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in rejected kidney, the homology to the conserved Fibulin-2 protein, in addition to the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting kidneys, particularly proliferative disorders. Representative uses are described here and elsewhere herein. The protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritus, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1920 of SEQ ID NO:67, b is an integer of 15 to 1934, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

Preferred polypeptides of the invention comprise the following amino acid sequence: MGEKFLLLAMKENHPECFCKILKILHCMDPGEWLPQTEHCVHLTPKEFLIWT MDIASNERSEIQSVALRLASKVISHHMQTCVENRELIAAELKQWVQLVILSCE DHLPTESRLAVVEVLTSTTPLFLTNPHPILELQDTLALWKCVLTLLQSEEQAV RDAATETVTTAMSQENTCQSTEFAFCQVDASIALALALAVLCDLLQQWDQL APGLPILLGWLLGESDDLVACVESMHQVEEDYLFEKAEVNFWAETLIFVKYL CKHLFCLLSKSGWRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTV EFTRLRIQEERTLACLRLLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAA C (SEQ ID NO: 246). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MGEPNRHPSM FLLLLVLERLYASPMDGTSSALSMGPFVPFIMRCGHSPVYHSREMAARALVP FVMIDHIPNTIRTLLSTL PSCTDQCFRAKPHSWGHFSRFFHLLQAYSDSKTRNEFRLPARAD (SEQ ID NO: 247). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: MTGREFFSRFPELYPFLLKQLETVANTVDSDMGEPNRHPSMFLLLLVLERLY ASPMDGTSSALSMGPFVPFIMRCGHSPVYHSREMAARALVPFVMIDHIPNTIR TLLSTLPSCTDQCFRQNHIHGTLLQVFHLLQAYSDSKHGTNSDFQHELTDITV CTKAKLWLAKRQNPCLVTRAVYIDILFLLTCCLNRSAKDNQPVLESLGFWEE VRGIISGSELITGFPWAFKVPGLPQYLQSLTRLAIAAVWAAAAKSGERETNVPI SFSQLLESAFPEVRSLTLEALLEKFLAAASGLGEKGVPPLLCNMGEKFLLLAM KENHPECFCKILKILHCMDPGEWLPQTEHCVHLTPKEFLIWTMDIASNERSEIQ SVALRLASKVISHHMQTCVENRELIAAELKQWVQLVILSCEDHLPTESRLAVV EVLTSTTPLFLTNPHPILELQDTLALWKCVLTLLQSEEQAVRDAATETVTTAM SQENTCQSTEFAFCQVDASIALALALAVLCDLLQQWDQLAPGLPILLGWLLG ESDDLVACVESMHQVEEDYLFEKAEVNFWAETLIFVKYLCKHLFCLLSKSG

WRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTVEFTRLRIQEERTL ACLRLLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAAC (SEQ ID NO: 248). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 144 - 160, and 462 - 478 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins. Included in this invention as a preferred domain is the formate and nitrite transporters domain, which was identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). A number of bacterial and archaebacterial proteins involved in transporting formate or nitrite have been shown [1] to be related: - focA and focB, from Escherichia coli, transporters involved in the bidirectional transport of formate. - fdhC, from Methanobacterium formicicum and thermoformicicum, a probable formate transporter. - nirC, from Escherichia coli and Salmonella typhimurium, a probable nitrite transporter. - Bacillus subtilis hypothetical protein yrhG. - Bacillus subtilis hypothetical protein ywcJ (ipa-48R). These transporters are proteins of about 280 residues and seem to contain six transmembrane regions. As signature patterns, we selected two conserved regions. The first one is located in what seems to be a cytoplasmic loop between the second and third transmembrane domains; the second is part of the fourth transmembrane region. The 70 Kd yeast hypothetical protein YHL008c is highly similar, in its N-terminal section, to the prokaryotic members of this family. The concensus pattern is as follows: [LIVMA]-[LIVMY]-x-G-[GSTA]-[DES]-L-[FI]-[TN]-[GS].

Preferred polypeptides of the invention comprise the following amino acid sequence: IISGSELITG (SEQ ID NO: 249). Polynucleotides encoding these polypeptides are also provided. Further preferred are polypeptides comprising the formate and nitrite transporter domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is N-terminal or C- terminal to the formate and nitrite transporter domain. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to

the formate and nitrite transporter domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to formate and nitrite transporter proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with formate and nitrite transporter proteins. Such activities are known in the art, some of which are described elsewhere herein. It is believed that this gene maps to chromosome 2. Accordingly, polynucleotides derived from this gene are useful in linkage analysis as markers for chromosome 2.

This gene is expressed primarily in cells of the immune system, primarily T-cells and to a lesser extent in spleen, liver, thymus, tonsils, and testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly disorders affecting hematopoesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of hematopoetic cells, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 160 as residues: Gly-2 to Pro-8, Ser-82 to His-92, Tyr-107 to Asp-117, Arg-162 to Pro-169, Ser-224 to Thr-229, Leu-310 to His-315, Ser-333 to Glu-338, Glu-381 to Ser-388, Gln-428 to Ala-433, Met-446 to Thr-455, Ser-548 to Ser-554, Gly-613 to Asp-618, Ser-627 to Gln-633. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoesis, including cancers. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3286 of SEQ ID NO:68, b is an integer of 15 to 3300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
VDGIDKLDIEFLQQFLETHSRGPRLHSPGHASQEATPGANMSSGTELLWPGAA
LLVLLGVAASLCVRCSRPGAKRSEKIYQQRSLREDQQSFTGSRTYSLVGQAW
PGPLADMAPTRKDKLLQFYPSLEDPASSRYQNFSKGSRHGSEEAYIDPIAMEY
YNWGRFSKPPEDDDANSYENVLICKQKTTETGAQQEGIGGLCRGDLSLSLAL
KTGPTSGLCPSASPEEDEGI (SEQ ID NO: 250). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 10 - 26 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in bone marrow, CD34 positive cells, and immune cells, including, neutrophils, T-cells, B-cells, macrophages, monocytes, and dendritic cells and to a lesser extent in brain and tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune and hematopoietic systems, particularly hematopoesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the the immune system and hematopoeitic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 161 as residues: Ser-29 to Thr-57, Pro-74 to Lys-79, Pro-85 to Glu-107, Tyr-118 to Tyr-136, Gln-144 to Gln-152, Ala-182 to Glu-188. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune and hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoesis. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for

immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities.

Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors);

hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures.

Based upon the the proteins immune cell specific message distribution, it may be involved

in many aspects of the immune response, especially its initial stages, inflammation, allograft rejection, infectious disease response etc. The expression of this clone is frequently found in the hematopoietic cell cDNA libraries. Thus, this factor could be involved in the control of hematopoietic cell proliferation, differentiation, and function. Based on this one can postulate its use in the management of anemias, leukemias, neutropenia, thrombocytopenia, autoimmune

diseases, blood tissue engraftment, and poikilothromerythromatosis. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1783 of SEQ ID NO:69, b is an integer of 15 to 1797, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: VLWREASALVLSNRLSSGLLHDLLLQPAIHSRLFPRRSRGLSEGEGSSVSLQRS RVLSAMKHVLNLYLLGVVLTLLSIFVRVMESLEGLLESPSPGTSWTTRSQLAN TEPTKGLPDHPSRSM (SEQ ID NO: 251). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in immune cells including activated T cells, macrophages, jurkat cells, bone marrow cells, and osteoblasts and to a lesser extent in kidney cortex, brain, placenta and lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly inflammation and diseases related to inflammatory activity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 162 as residues: Pro-34 to Met-63. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing disease related to the normal or abnormal activation of T cells.

Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:70, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
YTFHTQIFLDFPMIFLTVLPLAFLFLHSGFYHYISFSCLFSLSLALFFFLDVATFR
RPGQLFCERSVLFDMFHFGFVSLFLHEWIQAKHFWAGLF
IVLPSDVFFSVHHLEAPDGSFPNIAKLSLIILLR (SEQ ID NO: 252).
Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 2 - 18 and 22 - 38 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

This gene is expressed in many tissues including brain, liver, prostate, testes, cartilage, gall bladder. Expression is also seen in a number of tumors including colon carcinoma, pancreas tumor, osteoclastoma, ovarian cancer, B cell lymphoma and acute lymphocytic leukemias.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors of various organs including the pancreas, colon, and bone. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

major organs, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hepatic, metabolic, reproductive, testicular, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors and proliferative tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing tumors of several major organs including the pancreas and large intestine. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the

protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1565 of SEQ ID NO:71, b is an integer of 15 to 1579, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

This gene is expressed primarily in dendritic cells and fetal liver/spleen and to a lesser extent in many tissues including tonsils, fetal lung, stromal cell lines, bone marrow cell lines, placenta and tumors including hepatocellular carcinoma, pancreas tumor and osteosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune and hematopoietic system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic cells and fetal liver/spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnaosing and treating disorders of the immune system particularlly related to the control and generation of precursor cells. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:72, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in adrenal gland tumor and endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and vascular diseases and/or disorders, particularly diseases associated with the vascular endothelium. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating disorders that involve the vascular system including diseases such as atherschlerosis, neoangiogenesis associated with tumor growth and conditions associated with inflammation. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Alternatively, the protein is useful in the treatment, detection, and/or

prevention of metabolic disorders, particularly lethargy and depression. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3660 of SEQ ID NO:73, b is an integer of 15 to 3674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

The translation product of this gene is related to bovine PAM precursor. See Genbank record gi|163482 incorporated herein by reference. Moreover, see following patent publications are also incorporated herein by reference: J04311386 and WO8902460. Many bioactive peptides terminate with an amino acid alpha-amide at their COOH terminus. The enzyme responsible for this essential posttranslational modification is known as peptidyl-glycine alpha-amidating monooxygenase or PAM. An NH2-terminal signal sequence and short propeptide precede the NH2 terminus of purified PAM. The sequences of several PAM cyanogen bromide peptides were localized in the NH2-terminal half of the predicted protein. The forms of PAM purified from bovine neurointermediate pituitary is generated by endoproteolytic cleavage at a subset of the 10 pairs of basic amino acids in the precursor. High levels of PAM mRNA have been found in bovine pituitary and cerebral cortex. In

corticotropic tumor cells, levels of PAM mRNA and pro-ACTH/endorphin mRNA are known to be regulated in parallel by glucocorticoids and CRF.

This gene is expressed primarily in endometrial tumors, dendritic cells, a multiple sclerosis library, kidney, hematopoietic cells, melanocytes, osteoblasts, the spleen, colon, ovary, stromal cells, fetal and adult brain, heart, and in tissues undergoing wound repair.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometriosis, endometrial cancer, multiple sclerosis, hematopoietic diseases, bone disease, and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly the hematopoietic system and female reproduction. expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, immune, hematopoieticm integumentary, skeletal, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic and hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapuetic or diagnostic agent i's Diseases of hematopoietic origin as well as the female reproductive track due to the gene's primary pattern of expression. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses

include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2783 of SEQ ID NO:74, b is an integer of 15 to 2797, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65

The translation product of this gene shares sequence similarity with several G-protein coupled receptors (See Genbank Accession No. gb|AAC77910.1| (AF061443); all references available through this accession are hereby incorporated herein by reference; for example, Mol. Endocrinol. 12, 1830-1845 (1998)). G-protein coupled receptors are well known in the are and affect a variety of functions. In particular, the translation product of this gene shares similarity with Follical Stimulating Hormone Receptor.

Preferred polypeptides encoded by this gene comprise the following amino acid sequence: GTRFPTGETPSLGFTVTLVLLNSLAFLLMAVIYTKLYCNLEKEDLSENSQSSMIKHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFP (SEQ ID NO: 253). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MIKHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFPCLLA (SEQ ID NO: 254). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GTRFPTGETPSLGFTVTLVLLNSLAFLLMAVIYTKLYCNLEKEDLSENSQSSMIKHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFPLPACLNPVLYVFFNPKFKEDWKLLKRRVTKKSGSVSVSISSQGGCLEQDFYYDCGMYSHLQGNLTVCDCCESFLLTKPVSCKHLIKSHSCPALAVASCQRPEGYWSDCGTQSAHSDYADEEDSFVSDSSDQVQACGRACFYQSRGFPLVRYAYNLPRVKD (SEQ ID NO: 255). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 43 - 59 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 60 to 207 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins. Included in this invention as preferred domains are Zinc finger, C2H2 type domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). 'Zinc finger' domains [1-5] are nucleic acid-binding protein structures first identified in the Xenopus transcription factor TFIIIA. These domains have since been found in numerous nucleic acid-binding proteins. A zinc finger domain is composed of 25 to 30 amino-acid residues. There are two cysteine or histidine residues at both extremities of the domain, which are involved in the tetrahedral coordination of a zinc atom. It has been proposed that such a domain interacts with about five nucleotides. A schematic representation of a zinc finger domain is shown below:

```
          x x
         x   x
        x     x
        x     x
        x     x
         x   x
         C   H
        x \ / x
      x   Zn   x
        x / \ x
         C   H
 x x x x x     x x x x x
```

Many classes of zinc fingers are characterized according to the number and positions of the histidine and cysteine residues involved in the zinc atom

coordination. In the first class to be characterized, called C2H2, the first pair of zinc coordinating residues are cysteines, while the second pair are histidines. A number of experimental reports have demonstrated the zinc- dependent DNA or RNA binding property of some members of this class. Some of the proteins known to include C2H2-type zinc fingers are listed below. We have indicated, between brackets, the number of zinc finger regions found in each of these proteins; a '+' symbol indicates that only partial sequence data is available and that additional finger domains is present. In addition to the conserved zinc ligand residues it has been shown that a number of other positions are also important for the structural integrity of the C2H2 zinc fingers. The best conserved position is found four residues after the second cysteine; it is generally an aromatic or aliphatic residue. The concensus pattern is as follows: C-x(2,4)-C-x(3)-[LIVMFYWC]-x(8)-H-x(3,5)-H.

Preferred polypeptides of the invention comprise the following amino acid sequence: CDCCESFLLTKPVSCKHLIKSH (SEQ ID NO: 256). Polynucleotides encoding these polypeptides are also provided. Further preferred are polypeptides comprising the Zinc finger, C2H2 type domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is N-terminal or C- terminal to the Zinc finger, C2H2 type domain. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the Zinc finger, C2H2 type domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to zinc finger proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with G-coupled proteins, their receptors, and zinc finger proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in adult and fetal liver, human placenta, colon carcinoma cell lines and fibroblasts and to a lesser extent in the fetal and adult brain, the developing nervous system, lung, pancreas, salivary gland, breast tissue, and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the liver, developmental abnormalities, neurologic diseases, lung cancer, pancreatic cancer, and colon cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and hepatic origin, as well as the proliferation and/or differentiation of numerous types of tissues. expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, immune, hematopoietic, neural, gastrointestinal, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 167 as residues: Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for a diagnositic marker or therapeutic in a wide variety of disease states. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein expression in placental and brain tissue indicates the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. The protein is useful in the treatment, detection, and/or prevention of bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; pain; cancers; anorexia; bulimia; asthma; Parkinson's Disease; acute heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ulcers; allergies; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, severe mental retardation and dyskinesias, such as Huntington's Disease or Gilles de la Tourette's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2689 of SEQ ID NO:75, b is an integer of 15 to 2703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: ALENSGSPGLQDSARAHFNXSLRSFSFLRNQMYIFELSLYLEGTSFVVVLLFLL ISVSLDSPPTTKGWDSVLHIWVPLIVQ (SEQ ID NO: 257). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in placenta and in hematopoietic cells, especially those of T-cell and monocyte origin and to a lesser extent in the brain, endothelial cells, and the lungs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopietic, vascular, and developmental diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 168 as residues: Ser-30 to Trp-37. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in hematopoietic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic intervention in hematopoietic and developmental disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:76, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

This gene is expressed primarily in the prostate and to a lesser extent in in human B-cell lymphomas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer and diseases of hematopoietic origin, particularly of B-cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., prostate, reproductive, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 169 as residues: Asp-33 to Lys-42. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic or diagnostic marker for prostate cancer and disorders involving hematopoietic cells, especially

those of B-cell origin. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The protein is useful in modulating the immune response to aberrant proteins and polypeptides, as may exist in rapidly proliferating cells and tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1811 of SEQ ID NO:77, b is an integer of 15 to 1825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
GHESICGSCRSWIYFSIRCRRRMRPWWSLLLEACATCAQTGPTRSTSCTQEVS
HSSSTAYPAPMRRRCCL PSPRSCT (SEQ ID NO: 258). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

This gene is expressed primarily in the brain and the developing embryo and to a lesser extent in the heart, colon, adipose tissue, kidney, mammary tissue, activated T-cells and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases, developmental conditions, colon cancer, and hematopoietic diseases, especially of T-cell origin . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developmental, cardiovascular, adipose, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 170 as residues: Thr-18 to Cys-26, Glu-29 to Thr-36, Ser-50 to Thr-55. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain, combined with the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic agents in neurological diseases, developmental abnormalities, colon cancer, and hematopoietic diseases, especially those of T-cell origin. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal

cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:78, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 69

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: KRAGVEVGGLVMALAGSVFVLGGVLVLCVERNGEGEMGWPQHLPKSQPLS PPVAVRRCSFERSWIDLLVETSSSMVTCRQQVGTPNGMEGRGGGPKTTFPIRL QLSGACAVRPEIQWEV (SEQ ID NO: 259). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in activated monocytes, dendritic cells, and in the tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly leukemia, lymphomas, tumors of hematopoietic origin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 171 as residues: Gln-30 to Leu-38, Asn-75 to Thr-86. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in activated monocytes, dendritic cells, and tonsils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic and/or diagnostic agent for leukemias, lymphomas, and other diseases associated with cells of hematopoietic origin. Representative uses are described in the

"Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2177 of SEQ ID NO:79, b is an integer of 15 to 2191, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in the placenta, brain, and liver and to a lesser extent in most other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, neurological, vascular, and developmental diseases and/or disorders, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or

cell types (e.g., hematopoietic, neurological, vascular, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful therapeutic and/or diagnostic agent in a multitude of disease states, particularly those involving the immune and neurologic systems. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1321 of SEQ ID NO:80, b is an integer of 15 to 1335, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

The translation product of this gene shares sequence homology with the murine Fig1 (interleukin-four induced gene 1) which shares homology to the monoamine oxidases, particularly in domains responsible for FAD binding. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: QDWKAERSQDPFEKCMQDPDYEQLLKVTILEADNRIGGRIFTYRDQXTGWIG ELGAMRMPSSHRILHKLCQGLGLNLTKFTQYDKNTWTEVHEXKLRNYVVEK VPEKLGYALRPQEKGHSPEDIYQMALNQALKDLKALGCRKAMKKFERHTLL EYLLGEGNLSRPAVQLLGDVMSEDGFFYLSFAEALRAXSCLSDRLQYSRIVG GWDLLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQIETSPPARNLKVLKAD VVLLTASGPAVKRITFS (SEQ ID NO: 260), and/or LPRHMQEALRRLHYVPATKVFLSFRRPFWREEHIEGGHSNTDRPSRMIFYPPP REGALLLASYTWSDAAAAFAGLSREEALRLALDDVAALHGPVVRQLWDGT GVVKRWAEDQHSQGGFVVQXPALWQTEKDDWTVPYGRIYFAGEHTAYPHG WVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVASSPSH DLAKEEGS (SEQ ID NO: 261). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MAPLALHLLVLVPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVTIL EADNRIGGRIFTYRDQXTGWIGELGAMRMPSSHRILHKLCQGLGLNLTKFTQ YDKNTWTEVHEXKLRNYVVEKVPEKLGYALRPQEKGHSPEDIYQMALNQA LKDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDVMSEDGFFYL SFAEALRAXSCLSDRLQYSRIVGGWDLLPRALLSSLSGLVLLNAPVVAMTQG PHDVH VQIETSPPARNLKVLKADVVLLTASGPAVKRITFSPRCPATCRRRCGGCTTCR PPRCS (SEQ ID NO: 262). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with monoamine oxidases, disintegrins, metalloproteinases, and apoptosis modulating proteins. Such activities are known in the art, some of which are described elsewhere herein. Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 235 - 251 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 252 to 319 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in hematopoietic cells, particularly in dendritic cells, and activated monocytes and to a lesser extent in T-cells, endothelial cells, and cells associated with ulcerative colitis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemias, lymphomas, and diseases associated with antigen presenting cells, in addition to apoptosis dependant events. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression

of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 173 as residues: Gln-22 to Gln-44, Ala-90 to Gly-95, Lys-137 to Trp-146, Arg-171 to Asp-181, Glu-370 to Ser-380, Asp-447 to Gly-452, Gln-463 to Trp-469, Asn-504 to Ala-510, Asp-512 to His-519, Ala-541 to Val-550, Asn-558 to His-566. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution immune and hematopoietic cells and tissues, combined with the homology to the murine Fig 1 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic and/or diagnostic agent for hematopoietic diseases, especially those associated with antigen presenting cells. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatou's Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's

Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1853 of SEQ ID NO:81, b is an integer of 15 to 1867, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HISCN02	209878 05/18/98	pSport1	11	1113	1	1113	232	232	103	1	26	27	106
2	HHGDM70	209878 05/18/98	Lambda ZAP II	12	983	102	983	69	69	104	1	57	58	86
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	13	973	1	973	68	68	105	1	37	38	302
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	82	984	1	984	74	74	174	1	37	38	224
4	HAMGG68	209878 05/18/98	pCMVSport 3.0	14	1458	1	1458	312	312	106	1	20	21	55
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	15	2005	1	2005	251	251	107	1	22	23	189
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	83	2664	1	2664	448	448	175	1	1	2	123
6	HBGBA69	209878 05/18/98	Uni-ZAP XR	16	943	1	933	62	62	108	1	38	39	60
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	17	1503	588	1480	290	290	109	1	26	27	128

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	84	1328	413	1305	591	591	176	1	20	21	59
8	HCEDH38	209878 05/18/98	Uni-ZAP XR	18	1512	1	1438	222	222	110	1	26	27	68
9	HDPOJ08	209878 05/18/98	pCMVSport 3.0	19	1655	1	1655	159	159	111	1	18	19	122
10	HDPRX82	209878 05/18/98	pCMVSport 3.0	20	2525	1	2525	128	128	112	1	32	33	82
11	HELGK31	209878 05/18/98	Uni-ZAP XR	21	1396	25	1334	209	209	113	1	29	30	344
11	HCNUA40	97898 02/26/97 209044 05/15/97	pBluescript	85	1342	949	1237	960	960	177	1	33	34	105
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	22	1069	1	1069	181	181	114	1	28	29	181
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	86	1154	84	1154	257	257	178	1	28	29	87
12	HCEBW71	209225 08/28/97	Uni-ZAP XR	87	1197	141	1197	257	257	179	1	28	29	87

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
13	HFXDO60	209878 05/18/98	Lambda ZAP II	23	1658	1	1658	131	131	115	1	46	47	115
14	HHEPG41	209878 05/18/98	pCMVSport 3.0	24	1077	385	1043	514	514	116	1	35	36	70
14	HAUAI83	209626 02/12/98	Uni-ZAP XR	88	910	1	886	253	253	180	1	37	38	49
14	HJPAZ83	209626 02/12/98	Uni-ZAP XR	89	1076	398	1076		575	181	1	11	12	23
15	HKGAH42	209878 05/18/98	pSport1	25	1205	1	1205	143	143	117	1	21	22	63
16	HMIAP86	209878 05/18/98	Uni-ZAP XR	26	1674	13	1674	182	182	118	1	19	20	334
17	HMUAP70	209878 05/18/98	pCMVSport 3.0	27	1965	531	1914	183	183	119	1	16	17	221
17	HMUAP70	209878 05/18/98	pCMVSport 3.0	90	1842	407	1783	413	413	182	1	25	26	103
17	HAGFY16	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	91	1963	209	1922	251	251	183	1	28	29	198

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
17	HBMCF37	209683 03/20/98	pBluescript	92	1487	79	1487	170	170	184	1	44	45	70
17	HFLQB16	209641 02/25/98	Uni-ZAP XR	93	1653	394	1637	413	413	185	1	25	26	82
17	HAGFY16	97923 03/07/97	Uni-ZAP XR	94	1830	87	1786	128	128	186	1	26	27	45
18	HRACJ35	209878 05/18/98	pCMVSport 3.0	28	1863	8	1863	99	99	120	1	24	25	472
18	HAWAZ34	209141 07/09/97	pBluescript SK-	95	1134	472	1132	687	687	187	1			33
19	HTWDE26	209878 05/18/98	pSport1	29	1626	1	1626	68	68	121	1	30	31	167
19	HMHBN40	97901 02/26/97 209047 05/15/97	Uni-ZAP XR	96	1772	69	1772	129	129	188	1	30	31	231
20	HUSIB13	209878 05/18/98	pSport1	30	605	1	605	172	172	122	1	32	33	46
21	HBAFA02	209877 05/18/98	pSport1	31	931	359	931	46	46	123	1	21	22	108

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
22	H2CBT75	209877 05/18/98	pBluescript SK-	32	1407	1	1407	32	32	124	1	23	24	60
23	HAGDQ42	209877 05/18/98	Uni-ZAP XR	33	1526	1	1526	126	126	125	1	18	19	248
24	HBMCJ42	209877 05/18/98	pBluescript	34	1737	41	1580	244	244	126	1	44	45	248
25	HDPBQ71	209877 05/18/98	pCMVSport 3.0	35	2242	6	2242	24	24	127	1	33	34	612
26	HCEJG71	209877 05/18/98	Uni-ZAP XR	36	2235	2	2235	28	28	128	1	25	26	447
27	HELHL48	209877 05/18/98	Uni-ZAP XR	37	2971	560	2557	629	629	129	1	16	17	291
27	HSKCT36	209580 01/14/98	Uni-ZAP XR	98	1955	1	1955	31	31	190	1	18	19	184
28	HISAQ04	209877 05/18/98	pSport1	38	1163	1	1163	61	61	130	1	21	22	78
29	HJACB89	209877 05/18/98	pBluescript SK-	39	1932	28	1930	95	95	131	1	23	24	333
30	HTECC05	209877 05/18/98	Uni-ZAP XR	40	881	1	881	27	27	132	1	15	16	164

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
31	HBJLF01	209877 05/18/98	Uni-ZAP XR	41	1932	201	1931	217	217	133	1	46	47	244
32	HBXGP60	209877 05/18/98	ZAP Express	42	1164	1	1164	143	143	134	1	22	23	55
33	HCE5B20	209877 05/18/98	Uni-ZAP XR	43	1105	1	1105	237	237	135	1	25	26	54
34	HCMSQ56	209877 05/18/98	Uni-ZAP XR	44	1262	1	1262	148	148	136	1	19	20	88
35	HCNAH57	209877 05/18/98	Lambda ZAP II	45	517	1	517	35	35	137	1	33	34	61
36	HCUEP91	209877 05/18/98	ZAP Express	46	858	2	858	266	266	138	1	20	21	105
37	HDPCJ91	209877 05/18/98	pCMVSport 3.0	47	6107	1	6107	131	131	139	1	28	29	51
38	HDPGK25	209877 05/18/98	pCMVSport 3.0	48	703	1	703	345	345	140	1	33	34	119
39	HE2DY70	209877 05/18/98	Uni-ZAP XR	49	639	1	639	137	137	141	1	45	46	58
40	HE2NV57	209877 05/18/98	Uni-ZAP XR	50	867	1	867	99	99	142	1	36	37	99

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
41	HETBR16	209877 05/18/98	Uni-ZAP XR	51	1569	1	1569	161	161	143	1	21	22	64
42	HFXDG13	209877 05/18/98	Lambda ZAP II	52	1196	1	1196	43	43	144	1	37	38	66
43	HFXKY27	209877 05/18/98	Lambda ZAP II	53	945	1	945	44	44	145	1	19	20	58
44	HHPEC09	209877 05/18/98	Uni-ZAP XR	54	488	1	488	71	71	146	1	19	20	55
45	HISAD54	209877 05/18/98	pSport1	55	2860	1	2860	172	172	147	1	19	20	65
46	HJBCY35	209877 05/18/98	pBluescript SK-	56	1559	93	1272	232	232	148	1	23	24	327
47	HKAEA19	209877 05/18/98	pCMVSport 2.0	57	2064	1	1909	83	83	149	1	21	22	89
48	HKGDL36	209877 05/18/98	pSport1	58	1050	1	1050	55	55	150	1	33	34	148
49	HLDBS43	209877 05/18/98	pCMVSport 3.0	59	2533	1	2533	73	73	151	1	26	27	390
50	HLWAD92	209877 05/18/98	pCMVSport 3.0	60	899	1	899	197	197	152	1	34	35	98

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
51	HLYBI15	209877 05/18/98	pSport1	61	1079	1	1079	92	92	153	1	22	23	60
52	HMEJE05	209889 05/22/98	Lambda ZAP II	62	1928	1	1928	25	25	154	1	30	31	392
53	HNGIX55	209889 05/22/98	Uni-ZAP XR	63	781	1	781	121	121	155	1	19	20	74
54	HNHEX30	209889 05/22/98	Uni-ZAP XR	64	1194	1	1194	138	138	156	1	15	16	81
55	HPJBI33	209889 05/22/98	Uni-ZAP XR	65	1677	1	1677	236	236	157	1	31	32	53
56	HRABA80	209889 05/22/98	pCMVSport 3.0	66	1237	1	1237	130	130	158	1	28	29	102
57	HRACD80	209889 05/22/98	pCMVSport 3.0	67	1934	1	1934	191	191	159	1	16	17	575
57	HRACD80	209889 05/22/98	pCMVSport 3.0	99	1958	1	1958	191	191	191	1	16	17	146
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	68	3300	984	2729	677	677	160	1	22	23	643
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	100	2444	1	2444	392	392	192	1	22	23	124

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
59	HT5GJ57	209889 05/22/98	Uni-ZAP XR	69	1797	92	1797	122	122	161	1	25	26	190
60	HTACS42	209889 05/22/98	Uni-ZAP XR	70	1373	1	1373	213	213	162	1	29	30	63
61	HTEKE40	209889 05/22/98	Uni-ZAP XR	71	1579	1	1579	173	173	163	1	47	48	117
62	HTOBX69	209889 05/22/98	Uni-ZAP XR	72	1028	1	1028	28	28	164	1	20	21	42
63	HUVEO77	209889 05/22/98	Uni-ZAP XR	73	3674	1	3674	55	55	165	1	27	28	47
64	H2CBG48	209889 05/22/98	pBluescript SK-	74	2797	1	2797	125	125	166	1	25	26	45
65	H2CBU83	209889 05/22/98	pBluescript SK-	75	2703	1	2703	157	157	167	1	30	31	207
65	H2CBU83	209889 05/22/98	pBluescript SK-	101	2709	1	2709	157	157	193	1	30	31	51
66	HAPNY94	209889 05/22/98	Uni-ZAP XR	76	742	1	742	94	94	168	1	29	30	50
67	HBJHZ58	209889 05/22/98	Uni-ZAP XR	77	1825	1	1825	102	102	169	1	29	30	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
68	HCE2B33	209889 05/22/98	Uni-ZAP XR	78	1674	1	1668	67	67	170	1	18	19	55
69	HDPBQ02	209889 05/22/98	pCMVSport 3.0	79	2191	291	2191	460	460	171	1	24	25	108
70	HFIYI70	209889 05/22/98	pSport1	80	1335	1	1335	43	43	172	1	15	16	50
71	HDPOZ56	209889 05/22/98	pCMVSport 3.0	81	1867	415	1867	103	103	173	1	21	22	566
71	HDPOZ56	209889 05/22/98	pCMVSport 3.0	102	1722	1	1722	59	59	194	1	21	22	319

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly , the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further

below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed

sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

__Signal Sequences__

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the

information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown inTable 1, the ORF (open reading frame), or any fragement specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the presence invention can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignement of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95%

"identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is becuase the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the

query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter

the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See,

Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.

(Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

<u>Polynucleotide and Polypeptide Fragments</u>

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-

1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')2 fragments) which are capable of specifically binding to protein. Fab and F(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous

functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See,

D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The

expression constructs will further contain sites for transcription initiation. termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction. anion or cation exchange chromatography,

phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al.,

Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however,

polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques." Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression,

chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA

antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety

needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also

be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency,

Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

<u>Hyperproliferative Disorders</u>

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the

present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox , hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis,

opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See,

Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

__Chemotaxis__

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli.* Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity . and (b) determining if a biological activity of the polypeptide has been altered.

Other Activities

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in

the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino

acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is

expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library Plasmid	Corresponding Deposited
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain

XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for

bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with

phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to

manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.^{600}) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250

mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM

Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium

acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in

Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded

in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ^{35}S-methionine and 5 µCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a

chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo

contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

<u>Example 9: Protein Fusions</u>

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These

primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGT
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
ACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is

possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

<u>Example 11: Production Of Secreted Protein For High-Throughput Screening Assays</u>

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_20$; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,

Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

		JAKs			STATS	GAS(elements) or ISRE
Ligand	tyk2	Jak1	Jak2	Jak3		
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':<u>CTCGAG</u>ATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAA<u>AAGCTT</u>:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells

(ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell

Growth & Differentiation, 5:259-265) is used. First, harvest 2x10e^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

<u>Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.</u>

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 11, 37^oC for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

NF-κB (Nuclear Factor κB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-κB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- κB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κB is retained in the cytoplasm with I-κB (Inhibitor κB). However, upon stimulation, I- κB is phosphorylated and degraded, causing NF- κB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- κB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-κB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-kB would be useful in treating diseases. For example, inhibitors of NF-κB could be used to treat those diseases related to the acute or chronic activation of NF-kB, such as rheumatoid arthritis.

To construct a vector containing the NF-κB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-κB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:
5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-κB/SV40 fragment using XhoI and

HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-κB/SV40/SEAP cassette is removed from the above NF-κB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-κB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-κB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

__Example 17: Assay for SEAP Activity__

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 μl of 2.5x dilution buffer into Optiplates containing 35 μl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 μl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 μl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants

which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4 , 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;

and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St.

Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum. rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4; 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30^{o}C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37^{o}C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37^{o}C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine

phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv.

et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard

curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrastemal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector.

The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection

into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 28: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-

mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA

expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

__Example 29: Knock-Out Animals.__

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding

regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.,* see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

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B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 15, 1997	209044

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 179, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
August 28, 1997	209225

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer [illegible] International Division 703-[illegible]-2282	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 180, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
March 7, 1997	97923

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer Nicky Walker International Division 703-[illegible]	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description
on page 180 , line N/A .

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 22, 1997	209071

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer [illegible] [illegible] Division [illegible] [illegible]	Authorized officer

Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 180, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
February 12, 1998	209626

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer [illegible] International Division 703-[illegible]	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
March 20, 1998	209683

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer ... Division	Authorized officer

Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
February 25, 1998	209641

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
July 9, 1997	209141

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
February 26, 1997	97901

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer Division	Authorized officer

Form PCT/RO/134 (July 1992)

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 15, 1997	209047

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 181, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 18, 1998	209877

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer Misty Walker International Division 703-305-3032	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 182, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
January 14, 1998	209580

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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☒ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 185, line N/A.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
May 22, 1998	209889

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

Sequence Listing

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<213> Homo sapiens

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<213> Homo sapiens

<400> 15

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<211> 943
<212> DNA
<213> Homo sapiens

<400> 16

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<211> 1503
<212> DNA
<213> Homo sapiens

<400> 17

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<212> DNA
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<223> n equals a,t,g, or c

<220>
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<211> 1655
<212> DNA
<213> Homo sapiens

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<211> 2525
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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gccgc 2525

<210> 21
<211> 1396
<212> DNA
<213> Homo sapiens

<400> 21
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agctgctgtt tgaattatct gtgaatgttg ggaagaggaa tgccagagct gccggctgaa 180
aattacccaa ccaagagaaa tctgcaggat ggactttctg gtcctcttct tgttctacct 240
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<210> 22
<211> 1069
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (508)
<223> n equals a,t,g, or c

<400> 22

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accactagct tagaggttgc agtatgtttg gcatcttgcc atttgtgtta gttcagagga    180
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ggatcgcatg agcccgggag tttgaggctg cagtgagctg tgatcgcagc actgcactcc   1020
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<210> 23
<211> 1658
<212> DNA
<213> Homo sapiens

<400> 23

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tgccttctgg atgccctcat cctcctcggg gctggggtct ccctcaaggc cacccagctc    180
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ctgggcaagg agcactgagc agggagccgt gggagtagca actgggactg tgcttgacat     420
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<210> 24
<211> 1077
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1036)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1038)
<223> n equals a,t,g, or c

<400> 24

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cctacttcct gtttatcact tccgggttca tcattttggc atttcggtga tcgggttgga     180
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gaaatgcgag ggcctcgggt gttactctaa aatccgccct cagcttgcac gccggaagct     360
gcgattcctg cagcggaaga ggcgtgatct ggccttcgac tcgctatgtc cactaacaat     420
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tattcatttg ctttctcgtt gaaacctgtt gttaataaag tttttcactc tgaaaaaaaa 1020
aaaaaaaaaa aaaaancncg agggggggcc cggaacccaa ttcsccggat agtgagt 1077

<210> 25
<211> 1205
<212> DNA
<213> Homo sapiens

<400> 25
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ccttgtgggt gggggacagc aaatgaggga cctctctttt ctctacactc tcctttggct 180
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gtactgtcag gggatgaagt gtacttgtag tagagatgac gtcctgctgg atcagtcggc 420
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gataaatgag ggtgtcctgc tggataaatg agggggcccg tcaggtgaat ggagtgctgt 540
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<210> 26
<211> 1674
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1663)
<223> n equals a,t,g, or c

<400> 26
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aaactcgagg gggggcccgg tacccaattc gccctatggt gantcgaatg ggct 1674

<210> 27
<211> 1965
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (333)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1961)
<223> n equals a,t,g, or c

<400> 27
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atgatgtgct ttctgcccaa gtggtaattc atcttggttt gctatgttaa aactgtaaat 1860
acaacagaac attaataaat atctcttgtg tagcaccttt aaaaaaaaaa aaaaaaaaaa 1920
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa naaaa 1965

<210> 28
<211> 1863
<212> DNA
<213> Homo sapiens

<400> 28
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cgc 1863

<210> 29
<211> 1626
<212> DNA
<213> Homo sapiens

<400> 29
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<212> DNA
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<211> 2235
<212> DNA

<213> Homo sapiens

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 2971

<210> 38
<211> 1163
<212> DNA
<213> Homo sapiens

<400> 38
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gccttcgtgc ccagagtgac cccgtctgaa tgcagttctt tgcctcattc aaactgggga 180
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tggggctcac gggcaggggc tctgtgtccg gctggggcct ggggtcctgc gctgcacctg 480
tgtgtcagaa gcactcagta aatctttgct gatgaaggat gacaggatat aggacatgat 540

gcttgctgct gcattgcctg caatcctgga tgaatgccca ggttggcttt gctccccgtc 600
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aaaaaaaaaa aaaaaaaaaa aaa 1163

<210> 39
<211> 1932
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1624)
<223> n equals a,t,g, or c

<400> 39
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ctccagcggg ctgctgctca tgatcgagcg gggcatcctg gccgaratga agcccctgcc 180
cctgcacccg cccggccgcg arggcacagc ctggcgcggg aaagccccca agcctgggg 240
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cctgcgggcg gtgtgcggac agccaggcat gccccgggac ccctgggact tgccggtggg 360
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gctgccattt ttctgatgca tttatttaaa atttgtactt tttgatagaa cccttgtaag 1860
ggctttgttt tcctaatagc tgactttta ataaagcagt tttatataaa aaaaaaaaaa 1920
aaaaaaaaaa aa 1932

<210> 40
<211> 881
<212> DNA
<213> Homo sapiens

<400> 40
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ccattgaagg gaagaactgc ctccgctgct ggccagaact gtctgccttg atagactatg 120
acctgcagat cctctgggtg accccagggc cacccacaga actttctcaa agtattcact 180
ccttgttcct agaggataat aattttctca aaccctggta ccttgatcgt gaccatttgg 240
aagaagaaac agccaaattc ttcactcaag tacaccaagc cattaaaacg ttacgagatg 300
ataaaacagt acttctggaa gagatctaca cgcacaagaa tctctttact gagaggctga 360
ataagatatc tgatgggctg aaggagaagg gagccccacc cytctccatg aatgccttcc 420
cggctccatc tcctacttgc accccagaac cccttggctc tgtctgcctc cccagcacct 480
cagtttctct accttctcac ctccctggca gcctgcaatg agtcctgtgc caggaaccgg 540
cggacctccc tgtgggctgt gagtctcagc agtgctctac tcctggccat agctggagat 600
gtttctttta ctggcaaagg aagaaggagg cagtaaagga acagggcagc ccgcatgtct 660
tccagaagtg aacagaggcc gcagctacca ccgtcacaaa gttcactcat ctctgggtcc 720
cggtgacccc atccccccat accctccatc ctgggtcctg gggccccaaa gctctgaggc 780
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attaaaaccc ctcttcataa aaaaaaaaaa aaaaaactcg a 881

<210> 41
<211> 1932
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (2)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1022)
<223> n equals a,t,g, or c

<400> 41
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gggaaatagg cccccggggg cggtggcggc ggcggggcca tggcgcggag accccgggcg 120
ccggccgcct ccggggagga gttctccttc gtcagcccgc tggtgaaata cctgctcttc 180
ttcttcaaca tgctcttctg ggtgatttcc atggtgatgg tggctgtggg tgtctacgct 240
cggctaatga agcatgcaga agcagcccta gcctgcctgg cagtggaccc tgccatcctg 300
ctgatcgtgg tgggtgtcct catgttcctg ctcaccttct gtggctgcat tgggtccctc 360
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cagctggccg ctgggatcct gggcttcgtc ttctcagaca aggctcgagg gaaagtgagt 480
gagatcatca acaatgccat tgtgcactac cgagatgact tggatctgca gaacctcatt 540
gattttggcc agaaaaagtt tagctgctgt ggagggattt cctacaagga ctggtctcag 600
aacatgtatt tcaactgctc agaagacaac cccagtcgag agcgctgctc tgtgccttac 660
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ancagcacca aatggagatt tggattccag ccccccagtg acagcccagt gggaagaagc 1080

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ccaccccatt cccctgcatc ggagctcagt attcctacag ggtaagaggt aggaatcttg 1860
ctgggacgag gggagccaga agtggcaata aaagcgtgtt gacctggaaa aaaaaaaaaa 1920
aagggcggcc gc 1932

<210> 42
<211> 1164
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (582)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (592)
<223> n equals a,t,g, or c

<400> 42
ggcacgagct tgtgtgtcac cagcctcctg atctgccagg gtctgctctg ggttggcact 60
gaccagggtg tcatcgtcct gctgcccgtg cctcggctgg aaggcatccc caagatcaca 120
gggaaaggca tggtctcact caatgggcac tgtgggcctg tggccttcct ggctgtggct 180
accagcatcc tggcccctga catcctgcgg agtgaccagg aggaggctga ggggccccgg 240
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aagtctgtac atattggagc tctgggagat gctggaataa aagacaagag ttacatctgg 1140
acttggaaaa aaaaaaaaaa aaaa 1164

<210> 43
<211> 1105
<212> DNA

<213> Homo sapiens

<400> 43
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gagtcaattt ggtaatttat ttgtttctag gaatttgtcc atttcatcta gtttacctaa 180
tttttgacat ataaaattat atatggaaat ttctaaaata tttaaaaatt tctgtaatgt 240
caatagtaat gtcccctctt ttgttaccaa tttgttattt gaatcttctc cttttttttg 300
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ctttattatt tcattccttc tgggagcttt gggtctcatt ttttttccct gataatctag 480
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gtgttttaat ttgtattcat aactagaggg aaacagaggt gacggagaaa aagacgtaca 660
aatatcatcc acttgcaaag tatagatttg tttgtattgk ratatgaatr aaaatattac 720
gagacagata agaaaatttg aacactgacc attgatgcag ttacagttaa ttttaaaatc 780
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tgtttttaaa tgaaaagata tgcctgggat ttcttccaaa atgaatcttg taggttggga 900
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tacactaaag cttattttat cttattttac tgtatatact gttaaagctt gcattatttt 1020
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aaaaaaaaaa aaactcgagg ggggg 1105

<210> 44
<211> 1262
<212> DNA
<213> Homo sapiens

<400> 44
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tttctcgtga agcaagactt ctaaattatg gctataatat cttttgaatt gttgttctta 180
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gaacttgctg gagtaataga gggaaaacct ctgcctgatt ctaaatcaga tctttgtcct 360
atactcggac aattatggtt tcatatttta ttattttta ttttctgggt ttaacaaatg 420
agataacatt ttagacataa tatttgtaaa catcttgact tatttcagca ttttcctttt 480
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gccttatttc tgtgaaagaa atacagtatg tactttggga tttactaaag taaaactgtt 720
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<210> 45
<211> 517
<212> DNA
<213> Homo sapiens

<400> 45
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tctcagtgtg gcttttcatt atatttcctt gatgactaat ggtattcttt caccctttca 180
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ctaattatta ttattattat tatttgagat gaagtctcac tctgtcgccc aggcagaggt 420
tgcagtgggc cgagatagca ccactacact caagcctggc tgacagagtg agactctgtc 480
tcaaaaaaaa aaaaaaaaaa aaaaaaaaaa aactcga 517

<210> 46
<211> 858
<212> DNA
<213> Homo sapiens

<400> 46
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agcagggggc actaatggga ccaagctaac ctgtccagtg agaatcctgc agggagacct 180
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gagttggggg ccagccgcag aaacgagagc ccccgtgact ttgaggcacc ctttggagag 780
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ataactgagt ttctcgag 858

<210> 47
<211> 6107
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (5749)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5892)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5896)
<223> n equals a,t,g, or c

<220>
<221> SITE

<222> (5906)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5957)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5966)
<223> n equals a,t,g, or c

<400> 47
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ctttcactca gccaagtgtt agagtcagga aacccattga ggcaatggcg tcaaatggtg 120
tttcacaaga atgagccatt cagtctttgc tcactatata tttaatattt tattattgtt 180
gttattgtta ttattaattg gctttctgta ttctatgcct tttatttata aagacactaa 240
gaaaacccat gtttgtaatt ttaataacat ttttcccatc ttgtaatatc cagagctact 300
ttataaattc tctgaaccaa aagtattttc ctcagtgtat ctcttctccc ccagccccta 360
ttgggaaaaa ttacccagta tagttcaggt tatgaggagg atcagccaca caatccagtg 420
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<212> DNA
<213> Homo sapiens

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<211> 639
<212> DNA
<213> Homo sapiens

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<211> 867
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<210> 52
<211> 1196
<212> DNA
<213> Homo sapiens

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<221> SITE
<222> (590)
<223> n equals a,t,g, or c

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<211> 945
<212> DNA
<213> Homo sapiens

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<222> (295)
<223> n equals a,t,g, or c

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<221> SITE
<222> (875)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (914)
<223> n equals a,t,g, or c

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<213> Homo sapiens

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<211> 2860
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
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<211> 2064
<212> DNA
<213> Homo sapiens

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<220>
<221> SITE
<222> (2024)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2049)
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<212> DNA
<213> Homo sapiens

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<210> 59
<211> 2533
<212> DNA
<213> Homo sapiens

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<211> 899
<212> DNA
<213> Homo sapiens

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<212> DNA
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<211> 1928
<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

<400> 63
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g 781

<210> 64
<211> 1194
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1172)
<223> n equals a,t,g, or c

<400> 64
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ctatgtagaa cctgtccatg tggcccctcc ttgcagtctc cccatttggg ctggtttggg 180
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<210> 65
<211> 1677

<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1012)
<223> n equals a,t,g, or c

<400> 65
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tttaaaatta attttttgta gagatagggt ctcatatgtt gcccatgctg gtctcaaact 180
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tctggctgta gtgggaggga gcagaggagt gaatgattgt cagttgggag ggtgcagagt 360
gggctcctgc cctagggtgr aggtragggt ggcttaggtg asmcamcaca gaggccctgt 420
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gagtccagaa gttcaaaacc agactgggca acatagcaag accatctcta caaaaattaa 1560
ataaataaaa catttacaag ggttgtggtg aagattaaat gagatcactc acgaaaaagc 1620
tcagcagacc ctgatgtgca gtaggtgctc aataaatgtt agccagcaaa aaaaaag 1677

<210> 66
<211> 1237
<212> DNA
<213> Homo sapiens

<400> 66
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ctgggcagca tgacggtgcg ccggctgtca ctgctgtgcc gggacctctg ggcgctgtgg 180
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ctgggttttg ttgatgcttt tctaagaatg gagtactcgt tttcaagaga tttgtcctaa      960
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<210> 67
<211> 1934
<212> DNA
<213> Homo sapiens

<400> 67

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ggaggcacac tccggggtca gcagcatcca cagcagcatc cgccatgtcc cagcaaacgt      180
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gcgggcctca gctatcagct cggcctttga tccagaggcc gaggccctgc gcttccagct      660
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gggagagggc attg                                                       1934
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<210> 68
<211> 3300
<212> DNA
<213> Homo sapiens

<220>
<221> SITE

<222> (1)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (3)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (15)
<223> n equals a,t,g, or c

<400> 68
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ttcccgactg gaaagcgggc agtgagcgca acgcaattaa tgtgagttag ctcactcatt     180
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gataacaatt tcacacagga aacagctatg accatgatta cgccaagctc gaaattaacc     300
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<210> 69
<211> 1797
<212> DNA
<213> Homo sapiens

<400> 69
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<210> 70
<211> 1373
<212> DNA
<213> Homo sapiens

<400> 70
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<210> 71
<211> 1579
<212> DNA
<213> Homo sapiens

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caaaaaaaaa aaaaaaaaa 1579

<210> 72
<211> 1028
<212> DNA
<213> Homo sapiens

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<210> 73
<211> 3674
<212> DNA
<213> Homo sapiens

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<211> 2797
<212> DNA
<213> Homo sapiens

<220>
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<222> (853)
<223> n equals a,t,g, or c

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<211> 2703
<212> DNA
<213> Homo sapiens

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<211> 742
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<220>
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<222> (726)
<223> n equals a,t,g, or c

<400> 76

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<211> 1825
<212> DNA
<213> Homo sapiens

<400> 77

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<223> n equals a,t,g, or c

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<212> DNA
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<212> DNA
<213> Homo sapiens

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<211> 2664
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<211> 1328
<212> DNA
<213> Homo sapiens

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<210> 85
<211> 1342
<212> DNA
<213> Homo sapiens

<400> 85
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<210> 86
<211> 1154
<212> DNA
<213> Homo sapiens

<400> 86
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gaaactctgg ggtgaggcct ggttatctgc tgtaacagac cttccagtgg gttctgatgc 180
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<210> 87
<211> 1197
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (573)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1177)
<223> n equals a,t,g, or c

<220>
<221> SITE

<222> (1185)
<223> n equals a,t,g, or c

<400> 87
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gaaactctgg ggtgaggcct ggttatctgc tgtaacagac cttccagtgg gttctgatgc    180
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atcgcggcac tgcactccag tctgggcaac agagcaaaac cctgtctctt aaaaaaaaaa   1140
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<210> 88
<211> 910
<212> DNA
<213> Homo sapiens

<400> 88
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atcggggccc tgggaagcgc ctgtctatcc cgggggcagg acctgagcgc ccctgaccct    180
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acgccggact acatgaacct gctgggcatg atcttcagca tgtgcggcct catgcttaag    300
ctgaagtggt gtgcttgggt cgctgtctac tgctccttca tcagctttgc caactctcgg    360
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<210> 89
<211> 1076
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1029)

<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1037)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1040)
<223> n equals a,t,g, or c

<400> 89
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tattcatttg ctttctcgtt gaaacctgtt gttaataaag tttttcactc tgaaaaaaaa 1020
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<210> 90
<211> 1842
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (67)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (98)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (212)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1838)
<223> n equals a,t,g, or c

<400> 90
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gttgcagaat gaagaagagt ctggagaacc tgaacaggct gcaggtgatg ctcctccacc 180
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaanaa aa 1842

<210> 91
<211> 1963
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (335)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1959)
<223> n equals a,t,g, or c

<400> 91
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gaggaccaag gctgaagcta ctatcccttt ggttcctggg agagatgagg attttgtggg 480

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tgatgtgctt tctgcccaag tggtaattca tcttggtttg ctatgttaaa actgtaaata  1860
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<210> 92
<211> 1487
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1470)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1487)
<223> n equals a,t,g, or c

<400> 92

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cagttgcaga atgaagaaga gtctggagaa cctgaacagg ctgcaggtga tgctcctcca   180
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<210> 93
<211> 1653
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (67)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (212)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1636)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1653)
<223> n equals a,t,g, or c

<400> 93
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<213> Homo sapiens

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cactaacact ggaagccctc ttggaaagt tcttagcagc agactctgga cttggagaga 1200
agggcgtgcc acccttgctg tgcaacatgg gagagaagtt cttattgttg gccatgaagg 1260
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gactgcccat cctgctggga tggctgttgg gagagagtga tgacctcgtg gcctgtgtgg 1920
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agtgccacct cctgtctcag ttcttcagag agcttccacc agctgctgag tttgtgaaga 2160
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tggccttttt ggaaggaaag gaaggggaag acaccctagt tctcagtgtt tgggactctt 2280
atgcagaatc gaggcagtta actcttccaa gaacagaagc ggcatgttga agaaaatctg 2340
ggggattggg atgggggtat gtgtggattt ttcctccact aaatctgcag gaaacatgtt 2400
gaacataaat tcaaaaattt tatcccaaaa aaaaaaaaaa aaaa 2444

<210> 101
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 101
ggcacgagat ttcctacagg tgaaacgcca tcattaggat tcactgtaac gttagtgcta 60
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gaaaaagagg acctctcaga aaactcacaa tctagcatga ttaagcatgt cgcttggcta 180
atcttcacca attgcatctt tttctgccct gtggcgtttt tttcatttgc accattgatc 240
actgcaatct ctatcagccc cgaaataatg aagtctgtta ctctgatatt ttttccatgc 300
ctgcttgcct gaatccagtc ctgtatgttt tcttcaaccc aaagtttaaa gaagactgga 360
agttactgaa gcgacgtgtt accaagaaaa gtggatcagt ttcagtttcc atcagtagcc 420
aaggtggttg tctggaacag gatttctact acgactgtgg catgtactca catttgcagg 480
gcaacctgac tgtttgcgac tgctgcgaat cgtttctttt aacaaagcca gtatcatgca 540
aacacttgat aaaatcacac agctgtcctg cattggcagt ggcttcttgc caaagacctg 600
agggctactg gtccgactgt ggcacacatt cggcccactc tgattatgca gatgaagaag 660
attcctttgt ctcagacagt tctgaccagg tgcaggcctg tggacgagcc tgcttctacc 720
agagtagagg attccctttg gtgcgctatg cttacaatct accaagagtt aaagactgaa 780
ctactgtgtg tgtaaccgtt tcccccgtca accaaaatca gtgtttatag agtgaaccct 840
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taaaaattct atttttaaaa tgtgattttc tataactgaa gaaaaatatc ttgctaattt 1200
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ataaaagagc ctattcaata gctcagaggt tgaactctgg ttaaacaaga taatatgtta 1920
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acattgtcag tgtaataaaa acagaatctt tgtatatcaa aatcatgtag tttgtataaa 2400
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ttaaaaattg ctatcatgta tatttacaca tctgataaat attaaatcat aacttggtaa 2520
gaaactccta attaaaaggt tttttccaaa attcaggtta ttgaaaactt ttcattttat 2580
tcatttaaaa actagaataa cagatatata aaagtgttaa tctttgtgct atatggtatg 2640
aaatacaata ttgtactcag tgttttgaat tattaaagtt tctagaaagc aaaaaaaaaa 2700
aaaaaaaaa 2709

<210> 102
<211> 1722
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (401)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (695)
<223> n equals a,t,g, or c

<400> 102
gggaccgcgc tgtcctgctg tcaccaagag ctggagacac catctcccac cgagagtcat 60
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ccaggactgg aaggctgaac gcagccaaga cccccttcgag aaatgcatgc aggatcctga 180
ctatgagcag ctgctcaagg tcaccatcct ggaggcagat aacaggatcg gggccgcat 240
cttcacctac cgggaccaga wyacgggctg gattggggag ctgggagcca tgcgcatgcc 300
cagctctcac aggatcctcc acaagctctg ccagggcctg gggctcaacc tgaccaagtt 360
cacccagtac gacaagaaca cgtggacgga ggtgcacgaa ntgaagctgc gcaactatgt 420
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gcccgaagac atctaccaga tggctctcaa ccaggccctc aaagacctca aggcactggg 540
ctgcagaaag gcgatgaaga agtttgaaag gcacacgctc ttggaatatc ttctcgggga 600
ggggaacctg agccggccgg ccgtgcagct tctgggagac gtgatgtccg aggatggctt 660
cttctatctc agcttcgccg aggccctccg ggccnacagc tgcctcagcg acagactcca 720
gtacagccgc atcgtgggtg gctgggacct gctgccgcgc gcgctgctga gctcgctgtc 780
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gctgctgacg gcgagcggac cggcggtgaa gcgcatcacc ttctcgccgc gctgccccgc 960
cacatgcagg aggcgctgcg gaggctgcac tacgtgccgg ccaccaaggt gttcctaagc 1020
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ccgtcgcgca tgattttcta cccgccgccg cgcgagggcg cgctgctgct ggcctcgtac 1140
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gcgctcgacg acgtggcggc attgcacggg cctgtcgtgc gccagctctg ggacggcacc 1260
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ccggcgctct ggcaaaccga aaaggatgac tggacggtcc cttatggccg catctacttt 1380
gccggcgagc acaccgccta cccgcacggc tgggtggaga cggcggtcaa gtcggcgctg 1440
cgcgccgcca tcaagatcaa cagccggaag gggcctgcat cggacacggc cagccccgag 1500
gggcacgcat ctgacatgga ggggcagggg catgtgcatg ggtggccag cagcccctcg 1560
catgacctgg caaaggaaga aggcagccac cctccagtcc aaggccagtt atctctccaa 1620
aacacgaccc acacgaggac ctcgcattaa agtattttcg gaaaaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaagggcgg cc 1722

<210> 103
<211> 106
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (14)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 103
Met Gly Ser Leu Ser Gly Cys Ala Leu Pro Phe Cys Leu Xaa Val Phe
1 5 10 15

Phe Leu Thr Val Ser Pro Ser Ala Val Gly Leu Leu Xaa Phe Ala Gly
20 25 30

Gly Pro Leu Gln Thr Leu Phe Ala Trp Val Ser Pro Val Glu Ala Ala
35 40 45

Glu Gln Gln Arg Leu Leu Pro Val Leu Ser Ser Gly Ser Phe Val Ser
50 55 60

Glu Gly Thr Cys Gln Met Pro Ala Arg Ala Leu Leu Tyr Glu Val Ser
65 70 75 80

Val Gly Pro Tyr Trp Glu Ile Pro Pro Ser Gln Asp Thr Arg Arg Ser
85 90 95

Gly Thr Tyr Leu Arg Arg Gln Ser Asp Pro
100 105

<210> 104
<211> 86
<212> PRT
<213> Homo sapiens

<400> 104
Met Thr Leu Pro Ser Arg Ala Leu Ala Ser Leu Gly Val Gly Val Trp

1 5 10 15

Gly Met Leu Arg Leu Asn Gln Val Thr Val Ser Cys Gly Gly Ser Arg
20 25 30

Trp Ser Ser Arg Val Ala Leu Gly Ala Phe Ser Trp Val Cys Gly Val
35 40 45

Ala Leu Val Leu Gln Pro Ser Gly Gly Gly Leu Gly Leu Thr Ser Pro
50 55 60

Ser Glu Gly Cys Trp Glu Gly Glu Leu Ala Leu Ala Val Leu Arg Ala
65 70 75 80

Pro Gly Gly Ser Pro Ser
85

<210> 105
<211> 302
<212> PRT
<213> Homo sapiens

<400> 105
Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro Pro Gly Arg
1 5 10 15

Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
20 25 30

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
35 40 45

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
50 55 60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
65 70 75 80

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
85 90 95

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
100 105 110

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
115 120 125

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
130 135 140

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
145 150 155 160

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
165 170 175

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu

180 185 190

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
195 200 205

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
210 215 220

Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser Gly Asn Arg
225 230 235 240

Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr Ser Leu Arg
245 250 255

Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
260 265 270

Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
275 280 285

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg
290 295 300

<210> 106
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> Xaa equals stop translation

<400> 106
Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu Val
1 5 10 15

Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser Ala
20 25 30

Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg Gly
35 40 45

Arg Gly Leu Ile Ser Gly Gly Xaa
50 55

<210> 107
<211> 189
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (94)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 107
Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Leu Met
1 5 10 15

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
20 25 30

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
35 40 45

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
50 55 60

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
65 70 75 80

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
85 90 95

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
100 105 110

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
115 120 125

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
130 135 140

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
145 150 155 160

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
165 170 175

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
180 185

<210> 108
<211> 61
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (61)
<223> Xaa equals stop translation

<400> 108
Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
1 5 10 15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
20 25 30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
35 40 45

70

Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe Xaa
50 55 60

<210> 109
<211> 128
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 109
Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
1 5 10 15

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
20 25 30

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
35 40 45

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
50 55 60

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
65 70 75 80

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
85 90 95

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
100 105 110

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
115 120 125

<210> 110
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

<400> 110
Met Pro His Phe Leu Asp Trp Phe Val Pro Val Tyr Leu Val Ile Ser
1   5   10   15

Val Leu Ile Leu Val Gly Phe Gly Ala Cys Ile Tyr Tyr Phe Glu Pro
            20   25   30

Gly Leu Gln Glu Ala His Lys Trp Arg Met Gln Arg Pro Leu Val Asp
        35   40   45

Arg Xaa Leu Arg Lys Thr Leu Met Val Arg Asp Asn Leu Ala Phe Gly
    50   55   60

Gly Pro Glu Val Xaa
65

<210> 111
<211> 123
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (123)
<223> Xaa equals stop translation

<400> 111
Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile Cys Ala Leu Ala
1   5   10   15

Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu His Lys Glu Gln
            20   25   30

Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val Lys Asp Phe Ser
        35   40   45

Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys Tyr Tyr Val Ala
    50   55   60

Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe Thr Glu Lys Phe
65   70   75   80

Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser Val Val Tyr Val
                85   90   95

Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu Val Asp Lys Thr
            100   105   110

Gly Lys Asn Ile Ile Trp Val Leu Cys Ala Xaa
        115   120

<210> 112
<211> 83
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (83)
<223> Xaa equals stop translation

<400> 112
Met Glu Lys Gln Cys Cys Ser His Pro Val Ile Cys Ser Leu Ser Thr
1 5 10 15

Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Ser
20 25 30

Arg Ile Leu Leu Val Lys Tyr Ser Ala Asn Glu Gly Lys Leu Arg Leu
35 40 45

Gly Ile Cys Met Glu His Phe His Leu Ile Thr His Leu Ser Leu Ala
50 55 60

Phe Gly Ser Val Ile Tyr Asn Met Glu Ile Ile Met Pro Phe Ala Ser
65 70 75 80

Cys Glu Xaa

<210> 113
<211> 345
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (345)
<223> Xaa equals stop translation

<400> 113
Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Ser Val Leu Met
1 5 10 15

Gly Leu Val Leu Ile Cys Val Cys Ser Lys Thr His Ser Leu Lys Gly
20 25 30

Leu Ala Arg Gly Gly Ala Gln Ile Phe Ser Cys Ile Ile Pro Glu Cys
35 40 45

Leu Gln Arg Ala Xaa His Gly Leu Leu His Tyr Leu Phe His Thr Arg
50 55 60

Asn His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr
65 70 75 80

Thr Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu
85 90 95

Ser Leu His Tyr Leu Leu Leu Pro Tyr Leu Leu Leu Gly Val Asn Leu
100 105 110

Phe Phe Phe Thr Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys
115 120 125

Ala Asn Glu Leu Leu Phe Leu His Val Tyr Glu Phe Asp Glu Val Met
130 135 140

Phe Pro Lys Asn Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala
145 150 155 160

Arg Ser Lys His Cys Ser Val Cys Asn Trp Cys Val His Arg Phe Asp
165 170 175

His His Cys Val Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg
180 185 190

Tyr Phe Leu Ile Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val
195 200 205

Ala Ile Val Ser Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp
210 215 220

Leu Tyr Gln Glu Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met
225 230 235 240

Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile
245 250 255

Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly Gly
260 265 270

Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn
275 280 285

Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val
290 295 300

Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser
305 310 315 320

His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro
325 330 335

Cys His Glu Arg Lys Lys Gln Glu Xaa
340 345

<210> 114
<211> 181
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (110)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 114
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
35 40 45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
50 55 60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
65 70 75 80

Ser Leu Leu Gly Pro Phe Ile Lys Asn Gln Cys His Ser Ser Val Ile
85 90 95

Pro Leu Ser Asp Ser Ala Thr Ser Lys Ala Arg Ala Leu Xaa Leu Pro
100 105 110

Gly Arg Glu Thr Val Leu Ser Val Leu Pro Val Phe Ser Ser Pro Thr
115 120 125

Leu Pro Arg Thr His Ala Leu Gly Asp Ser Leu Gly Val Pro Gly Leu
130 135 140

Leu Val Cys Ser Glu Thr Ser Thr Leu Asn Asp His Trp Cys Cys Arg
145 150 155 160

Arg Ala Gly Ala Tyr Ile Pro Ile Asn Arg Arg Phe Ser His Leu Met
165 170 175

Pro Leu Ala Phe Ser
180

<210> 115
<211> 116
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (116)
<223> Xaa equals stop translation

<400> 115
Met Pro Ser Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
1 5 10 15

Ser Phe Leu Cys Leu Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
20 25 30

Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
35 40 45

Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
50 55 60

Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
65 70 75 80

Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
85 90 95

Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
100 105 110

Gly Gly Ile Xaa
115

<210> 116
<211> 71
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (71)
<223> Xaa equals stop translation

<400> 116
Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
35 40 45

Met Leu Ser Ile Ser Ala Val Val Met Ser Tyr Leu Gln Asn Pro Gln
50 55 60

Pro Met Thr Pro Pro Trp Xaa
65 70

<210> 117
<211> 64
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (64)

<223> Xaa equals stop translation

<400> 117
Met Arg Asp Leu Ser Phe Leu Tyr Thr Leu Leu Trp Leu Pro Glu Ile
1   5   10   15

Trp Gln Ala Leu Ala Gly Gly Ile Arg Leu Asp Glu Val Glu Leu Leu
            20   25   30

Glu Asn Glu Ala Val Leu Gly Glu Glu Met Arg Leu Tyr Arg Lys Ile
        35   40   45

Asn Glu Val Val Leu Ser Gly Asn Glu Val Val Leu Gly Gly Lys Xaa
    50   55   60

<210> 118
<211> 335
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (335)
<223> Xaa equals stop translation

<400> 118
Met Gly Ile Phe Pro Gly Ile Ile Leu Ile Phe Leu Arg Val Lys Phe
1   5   10   15

Ala Thr Ala Ala Val Ile Val Ser Gly Val Ser Lys His Leu His Cys
            20   25   30

Ile Ser His Gln Lys Ser Thr Thr Val Ser His Glu Met Ser Gly Leu
        35   40   45

Asn Trp Lys Pro Phe Val Tyr Gly Gly Leu Ala Ser Ile Val Ala Glu
    50   55   60

Phe Gly Thr Phe Pro Val Asp Leu Thr Lys Thr Arg Leu Gln Val Gln
65   70   75   80

Gly Gln Ser Ile Asp Ala Arg Phe Lys Glu Ile Lys Tyr Arg Gly Met
                85   90   95

Phe His Ala Leu Phe Arg Ile Cys Lys Glu Glu Gly Val Leu Ala Leu
            100   105   110

Tyr Ser Gly Ile Ala Pro Ala Leu Leu Arg Gln Ala Ser Tyr Gly Thr
        115   120   125

Ile Lys Ile Gly Ile Tyr Gln Ser Leu Lys Arg Leu Phe Val Glu Arg
    130   135   140

Leu Glu Asp Glu Thr Leu Leu Ile Asn Met Ile Cys Gly Val Val Ser

```
145                 150                 155                 160

Gly Val Ile Ser Ser Thr Ile Ala Asn Pro Thr Asp Val Leu Lys Ile
                165                 170                 175

Arg Met Gln Ala Gln Gly Ser Leu Phe Gln Gly Ser Met Ile Gly Ser
            180                 185                 190

Phe Ile Asp Ile Tyr Gln Gln Glu Gly Thr Arg Gly Leu Trp Arg Gly
        195                 200                 205

Val Val Pro Thr Ala Gln Arg Ala Ala Ile Val Val Gly Val Glu Leu
    210                 215                 220

Pro Val Tyr Asp Ile Thr Lys Lys His Leu Ile Leu Ser Gly Met Met
225                 230                 235                 240

Gly Asp Thr Ile Leu Thr His Phe Val Ser Ser Phe Thr Cys Gly Leu
                245                 250                 255

Ala Gly Ala Leu Ala Ser Asn Pro Val Asp Val Val Arg Thr Arg Met
            260                 265                 270

Met Asn Gln Arg Ala Ile Val Gly His Val Asp Leu Tyr Lys Gly Thr
        275                 280                 285

Val Asp Gly Ile Leu Lys Met Trp Lys His Glu Gly Phe Phe Ala Leu
    290                 295                 300

Tyr Lys Gly Phe Trp Pro Asn Trp Leu Arg Leu Gly Pro Trp Asn Ile
305                 310                 315                 320

Ile Phe Phe Ile Thr Tyr Glu Gln Leu Lys Arg Leu Gln Ile Xaa
                325                 330                 335


<210> 119
<211> 221
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 119
Met Ala Leu Ala Leu Ala Ala Leu Ala Ala Val Glu Pro Ala Cys Gly
  1               5                  10                  15

Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu
            20                  25                  30

Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile Ser Ala Glu
        35                  40                  45

Ser Ala Xaa Tyr Phe Asp Tyr Lys Asp Glu Ser Gly Phe Pro Lys Pro
    50                  55                  60
```

Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp Glu Ala Glu
65 70 75 80

Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly Arg Asp Glu
85 90 95

Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln Leu Arg Ile
100 105 110

Gly Asn Asp Gly Ile Phe Met Leu Thr Phe Phe Met Ala Phe Leu Phe
115 120 125

Asn Trp Ile Gly Phe Phe Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala
130 135 140

Gly Arg Tyr Gly Ala Ile Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp
145 150 155 160

Ile Leu Ile Val Arg Phe Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly
165 170 175

Gln Tyr Trp Leu Trp Trp Val Phe Leu Val Leu Gly Phe Leu Leu Phe
180 185 190

Leu Arg Gly Phe Ile Asn Tyr Ala Lys Val Arg Lys Met Pro Glu Thr
195 200 205

Phe Ser Asn Leu Pro Arg Thr Arg Val Leu Phe Ile Tyr
210 215 220

<210> 120
<211> 473
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (473)
<223> Xaa equals stop translation

<400> 120
Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
1 5 10 15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
20 25 30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys
35 40 45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
50 55 60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
65 70 75 80

```
Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
                85                  90                  95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
            100                 105                 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
        115                 120                 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
    130                 135                 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln
145                 150                 155                 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
                165                 170                 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val
            180                 185                 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
        195                 200                 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
    210                 215                 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225                 230                 235                 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
                245                 250                 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
            260                 265                 270

Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
        275                 280                 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
    290                 295                 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305                 310                 315                 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
                325                 330                 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
            340                 345                 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
        355                 360                 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
    370                 375                 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val
```

385 390 395 400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
405 410 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
420 425 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met
435 440 445

Asn Val Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp
450 455 460

Met Glu Glu Met Leu Pro Arg Ser Xaa
465 470

<210> 121
<211> 168
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (168)
<223> Xaa equals stop translation

<400> 121
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
20 25 30

Pro Pro Ser Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly
35 40 45

Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu
50 55 60

Arg Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile
65 70 75 80

Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro
85 90 95

Ile Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp
100 105 110

Asp Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu
115 120 125

Ala Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Ala
130 135 140

Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Ser Val Phe
145 150 155 160

```
Asp Arg His Val Val Leu Ser Xaa
                165


<210> 122
<211> 47
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals stop translation

<400> 122
Met Lys Phe Ile Leu Trp Arg Arg Phe Arg Trp Ala Ile Ile Leu Phe
  1               5                  10                  15

Ile Ile Leu Phe Ile Leu Leu Leu Phe Leu Ala Ile Phe Ile Tyr Ala
             20                  25                  30

Phe Pro Asn Tyr Ala Ala Met Lys Leu Val Lys Pro Phe Ser Xaa
         35                  40                  45


<210> 123
<211> 108
<212> PRT
<213> Homo sapiens

<400> 123
Met His Gln Asp Trp Leu Cys Asn Leu Gly Trp Pro Leu Leu Ser Leu
  1               5                  10                  15

Trp Ala Ala Glu Ser Ala Pro His Val Ala Met Ala Ser Ala Thr Ala
             20                  25                  30

Gln Leu Trp Ser Arg Pro Cys Gly Arg Thr His Met Val Ser Leu Ala
         35                  40                  45

Leu Gly His Gln Glu Thr Gly Leu Trp Leu Cys Ser Ala Phe Gly Cys
     50                  55                  60

Val Val Asp Ser Pro Trp Ala Ser Val Cys Pro Ser Val Lys Gly Gln
 65                  70                  75                  80

Leu Thr Val Cys Gly Ile Leu Pro Arg Val Pro Val Cys Val Tyr Val
                 85                  90                  95

Cys Ala Cys Val Arg Val Ser Met Cys Val His Ile
            100                 105


<210> 124
<211> 60
<212> PRT
<213> Homo sapiens
```

<400> 124
Met Arg Gly Cys Val Pro Ala Phe Leu Leu His Val Leu Ser Leu Arg
1 5 10 15

Arg Ala Cys Cys Thr Gln Ala Ala Gln Val Phe Thr Ala Gln Leu Pro
20 25 30

Gly Arg Gln Val Ala Arg Arg Arg Gly Gly Trp His Glu Gln Gln Gly
35 40 45

Gly Pro Met Leu Cys Ser Ser His His Ser Arg Thr
50 55 60

<210> 125
<211> 248
<212> PRT
<213> Homo sapiens

<400> 125
Met Ala Met Leu Pro Leu Val Leu His Trp Phe Phe Ile Glu Trp Tyr
1 5 10 15

Ser Gly Lys Lys Ser Ser Ser Ala Leu Phe Gln His Ile Thr Ala Leu
20 25 30

Phe Glu Cys Ser Met Ala Ala Ile Ile Thr Leu Leu Val Ser Asp Pro
35 40 45

Val Gly Val Leu Tyr Ile Arg Ser Cys Arg Val Leu Met Leu Ser Asp
50 55 60

Trp Tyr Thr Met Leu Tyr Asn Pro Ser Pro Asp Tyr Val Thr Thr Val
65 70 75 80

His Cys Thr His Glu Ala Val Tyr Pro Leu Tyr Thr Ile Val Phe Ile
85 90 95

Tyr Tyr Ala Phe Cys Leu Val Leu Met Met Leu Leu Arg Pro Leu Leu
100 105 110

Val Lys Lys Ile Ala Cys Gly Leu Gly Lys Ser Asp Arg Phe Lys Ser
115 120 125

Ile Tyr Ala Ala Leu Tyr Phe Phe Pro Ile Leu Thr Val Leu Gln Ala
130 135 140

Val Gly Gly Gly Leu Leu Tyr Tyr Ala Phe Pro Tyr Ile Ile Leu Val
145 150 155 160

Leu Ser Leu Val Thr Leu Ala Val Tyr Met Ser Ala Ser Glu Ile Glu
165 170 175

Asn Cys Tyr Asp Leu Leu Val Arg Lys Lys Arg Leu Ile Val Leu Phe
180 185 190

Ser His Trp Leu Leu His Ala Tyr Gly Ile Ile Ser Ile Ser Arg Val

195 200 205

Asp Lys Leu Glu Gln Asp Leu Pro Pro Leu Ala Leu Val Pro Thr Pro
210 215 220

Ala Leu Phe Tyr Leu Phe Thr Ala Lys Phe Thr Glu Pro Ser Arg Ile
225 230 235 240

Leu Ser Glu Gly Ala Asn Gly His
245

<210> 126
<211> 248
<212> PRT
<213> Homo sapiens

<400> 126
Met Glu Lys Ile Pro Glu Ile Gly Lys Phe Gly Glu Lys Ala Pro Pro
1 5 10 15

Ala Pro Ser His Val Trp Arg Pro Ala Ala Leu Phe Leu Thr Leu Leu
20 25 30

Cys Leu Leu Leu Leu Ile Gly Leu Gly Val Leu Ala Ser Met Phe His
35 40 45

Val Thr Leu Lys Ile Glu Met Lys Lys Met Asn Lys Leu Gln Asn Ile
50 55 60

Ser Glu Glu Leu Gln Arg Asn Ile Ser Leu Gln Leu Met Ser Asn Met
65 70 75 80

Asn Ile Ser Asn Lys Ile Arg Asn Leu Ser Thr Thr Leu Gln Thr Ile
85 90 95

Ala Thr Lys Leu Cys Arg Glu Leu Tyr Ser Lys Glu Gln Glu His Lys
100 105 110

Cys Lys Pro Cys Pro Arg Arg Trp Ile Trp His Lys Asp Ser Cys Tyr
115 120 125

Phe Leu Ser Asp Asp Val Gln Thr Trp Gln Glu Ser Lys Met Ala Cys
130 135 140

Ala Ala Gln Asn Ala Ser Leu Leu Lys Ile Asn Asn Lys Asn Ala Leu
145 150 155 160

Glu Phe Ile Lys Ser Gln Ser Arg Ser Tyr Asp Tyr Trp Leu Gly Leu
165 170 175

Ser Pro Glu Glu Asp Ser Thr Arg Gly Met Arg Val Asp Asn Ile Ile
180 185 190

Asn Ser Ser Ala Trp Val Ile Arg Asn Ala Pro Asp Leu Asn Asn Met
195 200 205

Tyr Cys Gly Tyr Ile Asn Arg Leu Tyr Val Gln Tyr Tyr His Cys Thr

```
        210                 215                 220

Tyr Lys Gln Arg Met Ile Cys Glu Lys Met Ala Asn Pro Val Gln Leu
225                 230                 235                 240

Gly Ser Thr Tyr Phe Arg Glu Ala
                245


<210> 127
<211> 612
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (245)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (246)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (249)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 127
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85                  90                  95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
```

145 150 155 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
165 170 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
180 185 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
195 200 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
210 215 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225 230 235 240

Asp Gly Asn Phe Xaa Xaa Ser Thr Xaa Leu Glu Lys Pro Gln Asn Met
245 250 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
260 265 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
275 280 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
290 295 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305 310 315 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
325 330 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
340 345 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
355 360 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
370 375 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385 390 395 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
405 410 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
420 425 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
435 440 445

Cys Ser Asn Asp Cys Pro Arg Lys Ile Thr Pro Phe Gly Val Asn Gln
450 455 460

Pro Gly Pro Tyr Ile Met Tyr Thr Thr Val Asp Ala Asn Gly Tyr Leu
465 470 475 480

Lys Asn Gly Ser Ala Gly Gln Leu Ser Gln Ser Ala His Leu Ala Leu
485 490 495

Gln Leu Pro Tyr Asn Val Leu Gly Leu Gly Arg Ser Ala Asn Phe Leu
500 505 510

Asp His Leu Tyr Val Gly Ile Pro Arg Pro Ser Gly Glu Lys Ser Ile
515 520 525

Arg Lys Gln Glu Trp Thr Ala Ile Ile Pro Asn Ser Gln Leu Ile Val
530 535 540

Ile Pro Tyr Pro His Asn Val Pro Arg Ser Trp Ser Ala Lys Leu Tyr
545 550 555 560

Leu Thr Pro Ser Asn Ile Val Leu Leu Thr Ala Ile Ala Leu Ile Gly
565 570 575

Val Cys Val Phe Ile Leu Ala Ile Ile Gly Ile Leu His Trp Gln Glu
580 585 590

Lys Lys Ala Asp Asp Arg Glu Lys Arg Gln Glu Ala His Arg Phe His
595 600 605

Phe Asp Ala Met
610

<210> 128
<211> 447
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (309)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (333)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 128

Met Glu Leu Ser Gln Met Ser Xaa Leu Met Gly Leu Ser Val Leu Leu
1 5 10 15

Gly Leu Leu Ala Leu Met Ala Thr Ala Ala Val Xaa Arg Gly Trp Leu
20 25 30

Arg Ala Gly Glu Glu Arg Ser Gly Arg Pro Ala Cys Gln Lys Ala Asn
35 40 45

Gly Phe Pro Pro Asp Lys Ser Ser Gly Ser Lys Lys Gln Lys Gln Tyr
50 55 60

Gln Arg Ile Arg Lys Glu Lys Pro Gln Gln His Asn Phe Thr His Arg
65 70 75 80

Leu Leu Ala Ala Ala Leu Lys Ser His Ser Gly Asn Ile Ser Cys Met
85 90 95

Asp Phe Ser Ser Asn Gly Lys Tyr Leu Ala Thr Cys Ala Asp Asp Arg
100 105 110

Thr Ile Arg Ile Trp Ser Thr Lys Asp Phe Leu Gln Arg Glu His Arg
115 120 125

Ser Met Arg Ala Asn Val Glu Leu Asp His Ala Thr Leu Val Arg Phe
130 135 140

Ser Pro Asp Cys Arg Ala Phe Ile Val Trp Leu Ala Asn Gly Asp Thr
145 150 155 160

Leu Arg Val Phe Lys Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe
165 170 175

Thr Ala Thr Pro Glu Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile
180 185 190

Asp Ile Gly Ile Ala Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser
195 200 205

Asp Thr Thr Val Leu Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr
210 215 220

Ile Asn Thr Asn Gln Met Asn Asn Thr His Ala Ala Val Ser Pro Cys
225 230 235 240

Gly Arg Phe Val Ala Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp
245 250 255

Glu Val Cys Phe Gly Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala
260 265 270

Phe Glu Leu Lys Gly His Ser Ala Ala Val His Ser Phe Ala Phe Ser
275 280 285

Asn Asp Ser Arg Arg Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys
290 295 300

Leu Trp Asp Thr Xaa Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu

305 310 315 320

Leu Lys Thr Gly Arg Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg
325 330 335

Leu Ala Leu Ser Pro Asn Ala Gln Val Leu Ala Leu Ala Ser Gly Ser
340 345 350

Ser Ile His Leu Tyr Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe
355 360 365

Glu Arg Val His Gly Glu Cys Ile Ala Asn Leu Ser Phe Asp Ile Thr
370 375 380

Gly Arg Phe Leu Ala Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His
385 390 395 400

Asn Thr Pro Gly His Arg Ala Met Val Glu Glu Met Gln Gly His Leu
405 410 415

Lys Arg Ala Ser Asn Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu
420 425 430

Thr Gln Ala Gln Glu Thr Leu Lys Ser Leu Gly Ala Leu Lys Lys
435 440 445

<210> 129
<211> 291
<212> PRT
<213> Homo sapiens

<400> 129
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
35 40 45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu

130 135 140

Thr Leu Lys Glu Thr Pro Gly Thr Val Leu Glu Val Leu Ile Cys Phe
145 150 155 160

Phe Thr Leu Trp Ser Val Val Gly Leu Thr Gly Phe His Thr Phe Leu
165 170 175

Val Ala Leu Asn Gln Thr Thr Asn Glu Asp Ile Lys Gly Ser Trp Thr
180 185 190

Gly Lys Asn Arg Val Gln Asn Pro Tyr Ser His Gly Asn Ile Val Lys
195 200 205

Asn Cys Cys Glu Val Leu Cys Gly Pro Leu Pro Pro Ser Val Leu Asp
210 215 220

Arg Arg Gly Ile Leu Pro Leu Glu Glu Ser Gly Ser Arg Pro Pro Ser
225 230 235 240

Thr Gln Glu Thr Ser Ser Ser Leu Leu Pro Gln Ser Pro Ala Pro Thr
245 250 255

Glu His Leu Asn Ser Asn Glu Met Pro Glu Asp Ser Ser Thr Pro Glu
260 265 270

Glu Met Pro Pro Pro Glu Pro Pro Glu Pro Pro Gln Glu Ala Ala Glu
275 280 285

Ala Glu Lys
290

<210> 130
<211> 78
<212> PRT
<213> Homo sapiens

<400> 130
Met Val Arg Lys Trp Leu Thr Phe Val Glu His Leu Leu Cys Ala Trp
1 5 10 15

Pro Arg Leu Gly Ala Phe Val Pro Arg Val Thr Pro Ser Glu Cys Ser
20 25 30

Ser Leu Pro His Ser Asn Trp Gly Val Gly Gly Arg Ala Ala Gln Leu
35 40 45

Thr Gly Ala Glu Leu Lys Thr His Ser Trp Val Cys Leu Gly Trp Ala
50 55 60

Val Leu Val Ala Pro Val Ala Asn Thr Arg Ala Pro Phe Thr
65 70 75

<210> 131
<211> 333
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (97)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 131
```
Met Leu Met Phe Ala Val Ile Val Ala Ser Ser Gly Leu Leu Leu Met
  1               5                  10                  15

Ile Glu Arg Gly Ile Leu Ala Glu Met Lys Pro Leu Pro Leu His Pro
             20                  25                  30

Pro Gly Arg Glu Gly Thr Ala Trp Arg Gly Lys Ala Pro Lys Pro Gly
         35                  40                  45

Gly Leu Ser Leu Arg Ala Gly Asp Ala Asp Leu Gln Val Arg Gln Asp
     50                  55                  60

Val Arg Asn Arg Thr Leu Arg Ala Val Cys Gly Gln Pro Gly Met Pro
 65                  70                  75                  80

Arg Asp Pro Trp Asp Leu Pro Val Gly Gln Arg Arg Thr Leu Leu Arg
                 85                  90                  95

Xaa Ile Leu Val Ser Asp Arg Tyr Arg Phe Leu Tyr Cys Tyr Val Pro
            100                 105                 110

Lys Val Ala Cys Ser Asn Trp Lys Arg Val Met Lys Val Leu Ala Gly
        115                 120                 125

Val Leu Asp Ser Val Asp Val Arg Leu Lys Met Asp His Arg Ser Asp
    130                 135                 140

Leu Val Phe Leu Ala Asp Leu Arg Pro Glu Glu Ile Arg Tyr Arg Leu
145                 150                 155                 160

Gln His Tyr Phe Lys Phe Leu Phe Val Arg Glu Pro Leu Glu Arg Leu
                165                 170                 175

Leu Ser Ala Tyr Arg Asn Lys Phe Gly Glu Ile Arg Glu Tyr Gln Gln
            180                 185                 190

Arg Tyr Gly Ala Glu Ile Val Arg Arg Tyr Arg Ala Gly Ala Gly Pro
        195                 200                 205

Ser Pro Ala Gly Asp Asp Val Thr Phe Pro Glu Phe Leu Arg Tyr Leu
    210                 215                 220

Val Asp Glu Asp Pro Glu Arg Met Asn Glu His Trp Met Pro Val Tyr
225                 230                 235                 240

His Leu Cys Gln Pro Cys Ala Val His Tyr Asp Phe Val Gly Ser Tyr
                245                 250                 255

Glu Arg Leu Glu Ala Asp Ala Asn Gln Val Leu Glu Trp Val Arg Ala
            260                 265                 270
```

Pro Pro His Val Arg Phe Pro Ala Arg Gln Ala Trp Tyr Arg Pro Ala
275 280 285

Ser Pro Glu Ser Leu His Tyr His Leu Cys Ser Ala Pro Arg Ala Leu
290 295 300

Leu Gln Asp Val Leu Pro Lys Tyr Ile Leu Asp Phe Ser Leu Phe Ala
305 310 315 320

Tyr Pro Leu Pro Asn Val Thr Lys Glu Ala Cys Gln Gln
325 330

<210> 132
<211> 164
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (126)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 132
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Xaa Ser Met
115 120 125

Asn Ala Phe Pro Ala Pro Ser Pro Thr Cys Thr Pro Glu Pro Leu Gly
130 135 140

Ser Val Cys Leu Pro Ser Thr Ser Val Ser Leu Pro Ser His Leu Pro
145 150 155 160

Gly Ser Leu Gln

<210> 133
<211> 245
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (245)
<223> Xaa equals stop translation

<400> 133
```
Met Val Ala Val Gly Val Tyr Ala Arg Leu Met Lys His Ala Glu Ala
 1               5                  10                  15

Ala Leu Ala Cys Leu Ala Val Asp Pro Ala Ile Leu Leu Ile Val Val
            20                  25                  30

Gly Val Leu Met Phe Leu Leu Thr Phe Cys Gly Cys Ile Gly Ser Leu
        35                  40                  45

Arg Glu Asn Ile Cys Leu Leu Gln Thr Phe Ser Leu Cys Leu Thr Ala
    50                  55                  60

Val Phe Leu Leu Gln Leu Ala Ala Gly Ile Leu Gly Phe Val Phe Ser
65                  70                  75                  80

Asp Lys Ala Arg Gly Lys Val Ser Glu Ile Ile Asn Asn Ala Ile Val
                85                  90                  95

His Tyr Arg Asp Asp Leu Asp Leu Gln Asn Leu Ile Asp Phe Gly Gln
            100                 105                 110

Lys Lys Phe Ser Cys Cys Gly Gly Ile Ser Tyr Lys Asp Trp Ser Gln
        115                 120                 125

Asn Met Tyr Phe Asn Cys Ser Glu Asp Asn Pro Ser Arg Glu Arg Cys
    130                 135                 140

Ser Val Pro Tyr Ser Cys Cys Leu Pro Thr Pro Asp Gln Ala Val Ile
145                 150                 155                 160

Asn Thr Met Cys Gly Gln Gly Met Gln Ala Phe Asp Tyr Leu Glu Ala
                165                 170                 175

Ser Lys Val Ile Tyr Thr Asn Gly Cys Ile Asp Lys Leu Val Asn Trp
            180                 185                 190

Ile His Ser Asn Leu Phe Leu Leu Gly Gly Val Ala Leu Gly Leu Ala
        195                 200                 205

Ile Pro Gln Leu Val Gly Ile Leu Leu Ser Gln Ile Leu Val Asn Gln
    210                 215                 220

Ile Lys Asp Gln Ile Lys Leu Gln Leu Tyr Asn Gln Gln His Arg Ala
225                 230                 235                 240

Asp Pro Trp Tyr Xaa
```

245

<210> 134
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> Xaa equals stop translation

<400> 134
Met Gly Thr Val Gly Leu Trp Pro Ser Trp Leu Trp Leu Pro Ala Ser
1 5 10 15

Trp Pro Leu Thr Ser Cys Gly Val Thr Arg Arg Arg Leu Arg Gly Pro
20 25 30

Gly Leu Arg Arg Thr Ser Gln Thr Gly Arg His Thr Ser Pro Cys Pro
35 40 45

Thr Ala Thr Trp Ala Glu Ser Xaa
50 55

<210> 135
<211> 55
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (55)
<223> Xaa equals stop translation

<400> 135
Met Ser Ile Val Met Ser Pro Leu Leu Leu Pro Ile Cys Tyr Leu Asn
1 5 10 15

Leu Leu Leu Phe Phe Val Asn Leu Ala Lys Asn Leu Ser Ile Leu Phe
20 25 30

Val Ser Ser Lys Lys Tyr Thr Phe Val Phe Met Ile Ser Leu Xaa Phe
35 40 45

Phe His Xaa Tyr Phe Ile Xaa

50 55

<210> 136
<211> 89
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (89)
<223> Xaa equals stop translation

<400> 136
Met Ala Ile Ile Ser Phe Glu Leu Leu Phe Leu Met Asn Leu Pro Thr
1 5 10 15

Val Asn Ser Ser Asn Phe Lys Leu Ile Ile Pro Glu Asp Val Thr Leu
20 25 30

Ser Phe Val Ser His Leu Asp Ile Thr Val Asn His Phe Val Phe Leu
35 40 45

Ser Thr Phe Glu Leu Ala Gly Val Ile Glu Gly Lys Pro Leu Pro Asp
50 55 60

Ser Lys Ser Asp Leu Cys Pro Ile Leu Gly Gln Leu Trp Phe His Ile
65 70 75 80

Leu Leu Phe Phe Ile Phe Trp Val Xaa
85

<210> 137
<211> 62
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (62)
<223> Xaa equals stop translation

<400> 137
Met Arg Leu Pro Ile Ala Pro His Leu Gln Tyr Phe Met Trp Ser Val
1 5 10 15

Leu Leu Phe Leu Val Ile Leu Val Asp Met Lys Trp His Leu Ser Val
20 25 30

Ala Phe His Tyr Ile Ser Leu Met Thr Asn Gly Ile Leu Ser Pro Phe
35 40 45

Gln Cys Leu Leu Ala Ile His Val Ser Leu Phe Phe Val Xaa
50 55 60

<210> 138

<211> 106
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (106)
<223> Xaa equals stop translation

<400> 138
Met Cys Leu Leu Pro Gly Gly Val Leu Leu Ile Trp Ser Cys Ala Ser
1 5 10 15

Gly Thr Pro Ala Ser His Thr Lys Asp Trp Gly Arg Cys Lys Phe Ser
20 25 30

Ala Ala Thr Lys Arg Thr Ala Glu Ser Asn Leu Glu Ser Thr Gln Leu
35 40 45

Met Leu Ala Ser Gln Ile Asp Pro Leu Leu Ala Glu Cys Trp His Leu
50 55 60

Cys Ala Ser Val Ser Ser Ser Val Asn Gly Gly Asp Lys Lys Cys Val
65 70 75 80

His Thr Ser Arg Ala Val Gly Arg Ile Lys Leu Cys Ser Asp Thr Ile
85 90 95

Arg Ala Cys Ser Gly Trp Tyr Leu Gln Xaa
100 105

<210> 139
<211> 52
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (52)
<223> Xaa equals stop translation

<400> 139
Met Ser His Ser Val Phe Ala His Tyr Ile Phe Asn Ile Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Ile Gly Phe Leu Tyr Ser Met Pro Phe Ile
20 25 30

Tyr Lys Asp Thr Lys Lys Thr His Val Cys Asn Phe Asn Asn Ile Phe
35 40 45

Pro Ile Leu Xaa
50

<210> 140
<211> 119

<212> PRT
<213> Homo sapiens

<400> 140
Met Lys Trp Arg Arg Lys Ser Ala Tyr Trp Lys Ala Leu Lys Val Phe
1 5 10 15

Lys Leu Pro Val Glu Phe Leu Leu Leu Leu Thr Val Pro Val Val Asp
20 25 30

Pro Asp Lys Asp Asp Gln Asn Trp Lys Arg Pro Leu Asn Cys Leu His
35 40 45

Leu Val Ile Ser Pro Leu Val Val Val Leu Thr Leu Gln Ser Gly Thr
50 55 60

Tyr Gly Val Tyr Glu Ile Gly Gly Leu Val Pro Val Trp Val Val Val
65 70 75 80

Val Ile Ala Gly Thr Ala Leu Ala Ser Val Thr Phe Phe Ala Thr Ser
85 90 95

Asp Ser Gln Pro Pro Arg Leu His Trp Leu Phe Ala Phe Leu Gly Phe
100 105 110

Leu Thr Ser Ala Leu Trp Ile
115

<210> 141
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (59)
<223> Xaa equals stop translation

<400> 141
Met Cys Ser Gly Ser Phe Lys Glu Leu Tyr Leu Val Pro Ile Ser Leu
1 5 10 15

Phe Ser Thr Cys Val Leu Gly Phe Tyr Phe His Asn Phe Leu Leu Leu
20 25 30

Ile Ile Leu Phe Ser Ile Leu Leu Arg Lys Ile Thr Gly Lys Leu Phe
35 40 45

Phe Thr Tyr Tyr His Phe Ser Cys Gly Val Xaa
50 55

<210> 142
<211> 100
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (100)
<223> Xaa equals stop translation

<400> 142
Met Leu Phe Phe Leu Ser Leu Phe Leu Ser Leu Leu Leu Thr Leu Ser
1 5 10 15

Leu Pro Ser Phe Leu Pro Phe Ser Phe Phe Phe Phe Ser Leu Phe Pro
20 25 30

His Leu Ser Ala Cys Leu Leu Pro Ser Leu Pro Ser Pro Pro Phe Pro
35 40 45

Leu Pro Pro Ser Leu Pro Ser Phe Leu Pro Ser Phe Leu Pro Ser Phe
50 55 60

Leu Pro Ser Leu Leu Ser Pro Ser Phe Pro Ala Phe Phe Pro Ser Phe
65 70 75 80

Cys Gln Leu Ala Arg Arg Ser Pro Arg Lys Ser Thr Gln Met Leu Gln
85 90 95

Ser Thr Ser Xaa
100

<210> 143
<211> 65
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (65)
<223> Xaa equals stop translation

<400> 143
Met Ala Val Leu Leu Ile Thr Ile Leu Leu Phe Leu Cys Leu Gly Tyr
1 5 10 15

Tyr Arg Val Ile Thr Glu Ile Ser Arg Lys Thr Pro Ala Cys Arg Met
20 25 30

Phe Thr Ser Ser Leu Ser Ser Trp Tyr Ile Met Arg Lys Leu Tyr Asp
35 40 45

Thr Pro Gly Glu Val Phe Leu Ser His Ala Ile Val Xaa Phe Leu Lys
50 55 60

Xaa
65

<210> 144
<211> 67
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (67)
<223> Xaa equals stop translation

<400> 144
Met Leu Asn Gln Pro Cys Ile Leu Gly Met Lys Pro Thr Trp Leu Trp
1 5 10 15

Trp Ile Ser Phe Leu Met Cys Cys Trp Val Trp Leu Ala Ser Val Leu
20 25 30

Leu Gly Ile Phe Ala Ser Ile Phe Ile Arg Asp Ile Gly Leu Glu Phe
35 40 45

Ser Phe Phe Val Met Cys Leu Pro Gly Phe Gly Ile Arg Val Met Leu
50 55 60

Ala Ser Xaa
65

<210> 145
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (59)
<223> Xaa equals stop translation

<400> 145
Met Thr Ala Met Ser Ile His Leu Phe Cys Thr Ala Leu Ser Cys Gly
1 5 10 15

Ser Ser Gly Gln Cys Asn Lys Ala Ile Lys Arg Asn Lys Ile Ser Asn
20 25 30

Asp Trp Lys Asp Val Asn Val Ser Ser Phe Ile Glu Asn Met Ile His
35 40 45

Arg Tyr Thr Tyr Thr Asn Ala Leu Asn Ser Xaa
50 55

<210> 146
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> Xaa equals stop translation

<400> 146
Met Ser His Cys Thr Trp Pro Val Cys Leu Phe Cys Leu Val Pro Pro
1 5 10 15

Pro Met Gly Asp Leu Lys Glu Val Cys Leu Pro His Arg Cys Pro Gly
20 25 30

Arg Thr Ala Cys Cys Ser Tyr Ser Glu Pro His Leu Gln Thr Glu Glu
35 40 45

Asp Arg Arg Thr Leu Ile Cys Xaa
50 55

<210> 147
<211> 66
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (66)
<223> Xaa equals stop translation

<400> 147
Met Thr Asn Gly His Gln Val Leu Leu Leu Leu Leu Leu Thr Ser Ala
1 5 10 15

Val Ala Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp
20 25 30

Met Cys Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu
35 40 45

Gly Gly Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly
50 55 60

Tyr Xaa
65

<210> 148
<211> 328
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (328)
<223> Xaa equals stop translation

<400> 148
Met Ala Cys Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg

1 5 10 15

His Leu Pro Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn
20 25 30

Phe Gln Glu Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val
35 40 45

Leu Gly Leu Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His
50 55 60

Gln Gly Ala Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu
65 70 75 80

Asn Tyr Arg Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe
85 90 95

Val Gln Phe Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile
100 105 110

Ser Phe Leu Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp
115 120 125

Asn Ser Asp Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu
130 135 140

Pro Ser Arg Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu
145 150 155 160

Glu Glu Ser Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe
165 170 175

Thr Pro Leu Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser
180 185 190

Arg Gly Gln Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp
195 200 205

Glu Met Ser Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn
210 215 220

Leu Gln Arg Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala
225 230 235 240

Phe Ser Leu Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala
245 250 255

Ala Phe Leu Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu
260 265 270

Val Val Gln Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys
275 280 285

Gln Glu His Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met
290 295 300

Tyr Gly Gln Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile
305 310 315 320

Leu His Met Glu Ala Val Met Xaa
325

<210> 149
<211> 90
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals stop translation

<400> 149
Met Gly Phe Leu Gln Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His
1 5 10 15

Arg Val Ala Gly Ala Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu
20 25 30

Ile Glu Phe Ser Val Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro
35 40 45

Phe Pro Glu Glu Ala Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe
50 55 60

Leu Ile Phe Gln Ile His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe
65 70 75 80

Ser Pro Arg Arg Arg Ser Pro Thr Met Xaa
85 90

<210> 150
<211> 149
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (149)
<223> Xaa equals stop translation

<400> 150
Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly
1 5 10 15

Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu
20 25 30

Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala Ser Pro
35 40 45

Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln Cys Pro
50 55 60

Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala Gly Ala
65 70 75 80

Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala Gln Arg
85 90 95

Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala Ser Gly
100 105 110

Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr Thr Pro
115 120 125

Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro Ala Leu
130 135 140

Thr Leu Pro Pro Xaa
145

<210> 151
<211> 391
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (391)
<223> Xaa equals stop translation

<400> 151
Met Leu Pro Thr Trp Trp Ile Val Ser Ser Trp Leu Val Trp Gly Val
1 5 10 15

Ile Leu Phe Val Tyr Leu Val Ile Arg Ala Leu Arg Leu Trp Arg Thr
20 25 30

Ala Lys Leu Gln Val Thr Leu Lys Lys Tyr Ser Val His Leu Glu Asp
35 40 45

Met Ala Thr Asn Ser Arg Ala Phe Thr Asn Leu Val Arg Lys Ala Leu
50 55 60

Arg Leu Ile Gln Glu Thr Glu Val Ile Ser Arg Gly Phe Thr Leu Val
65 70 75 80

Ser Ala Ala Cys Pro Phe Asn Lys Ala Gly Gln His Pro Ser Gln His
85 90 95

Leu Ile Gly Leu Arg Lys Ala Val Tyr Arg Thr Leu Arg Ala Asn Phe
100 105 110

Gln Ala Ala Arg Leu Ala Thr Leu Tyr Met Leu Lys Asn Tyr Pro Leu
115 120 125

Asn Ser Glu Ser Asp Asn Val Thr Asn Tyr Ile Cys Val Val Pro Phe
130 135 140

Lys Glu Leu Gly Leu Gly Leu Ser Glu Glu Gln Ile Ser Glu Glu Glu
145 150 155 160

Ala His Asn Phe Thr Asp Gly Phe Ser Leu Pro Ala Leu Lys Val Leu
165 170 175

Phe Gln Leu Trp Val Ala Gln Ser Ser Glu Phe Phe Arg Arg Leu Ala
180 185 190

Leu Leu Leu Ser Thr Ala Asn Ser Pro Pro Gly Pro Leu Leu Thr Pro
195 200 205

Ala Leu Leu Pro His Arg Ile Leu Ser Asp Val Thr Gln Gly Leu Pro
210 215 220

His Ala His Ser Ala Cys Leu Glu Glu Leu Lys Arg Ser Tyr Glu Phe
225 230 235 240

Tyr Arg Tyr Phe Glu Thr Gln His Gln Ser Val Pro Gln Cys Leu Ser
245 250 255

Lys Thr Gln Gln Lys Ser Arg Glu Leu Asn Asn Val His Thr Ala Val
260 265 270

Arg Ser Leu Gln Leu His Leu Lys Ala Leu Leu Asn Glu Val Ile Ile
275 280 285

Leu Glu Asp Glu Leu Glu Lys Leu Val Cys Thr Lys Glu Thr Gln Glu
290 295 300

Leu Val Ser Glu Ala Tyr Pro Ile Leu Glu Gln Lys Leu Lys Leu Ile
305 310 315 320

Gln Pro His Val Gln Ala Ser Asn Asn Cys Trp Glu Glu Ala Ile Ser
325 330 335

Gln Val Asp Lys Leu Leu Arg Arg Asn Thr Asp Lys Lys Gly Lys Pro
340 345 350

Glu Ile Ala Cys Glu Asn Pro His Cys Thr Val Ser Thr Phe Glu Ala
355 360 365

Ala Tyr Ser Thr His Cys Arg Gln Arg Ser Asn Pro Arg Gly Ala Gly
370 375 380

Ile Arg Ser Leu Cys Arg Xaa
385 390

<210> 152
<211> 99
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (99)
<223> Xaa equals stop translation

<400> 152
Met Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met
1 5 10 15

Ser Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser
20 25 30

Leu Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp
35 40 45

Asn Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu
50 55 60

Gly Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr
65 70 75 80

Gln Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu
85 90 95

Val Thr Xaa

<210> 153
<211> 61
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (61)
<223> Xaa equals stop translation

<400> 153
Met Ser His Cys Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser
1 5 10 15

Cys Phe Trp Ala Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val
20 25 30

Ser Phe Arg Pro Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe
35 40 45

Ile Leu Arg Ile Leu Ile Leu Leu Arg Ser Phe Leu Xaa
50 55 60

<210> 154

<211> 393
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (393)
<223> Xaa equals stop translation

<400> 154
Met Glu Trp Trp Ala Ser Ser Pro Leu Arg Leu Trp Leu Leu Leu Phe
1 5 10 15

Leu Leu Pro Ser Ala Gln Gly Arg Gln Lys Glu Ser Gly Ser Lys Trp
20 25 30

Lys Val Phe Ile Asp Gln Ile Asn Arg Ser Leu Glu Asn Tyr Glu Pro
35 40 45

Cys Ser Ser Gln Asn Cys Ser Cys Tyr His Gly Val Ile Glu Glu Asp
50 55 60

Leu Thr Pro Phe Arg Gly Gly Ile Ser Arg Lys Met Met Ala Glu Val
65 70 75 80

Val Arg Arg Lys Leu Gly Thr His Tyr Gln Ile Thr Lys Asn Arg Leu
85 90 95

Tyr Arg Glu Asn Asp Cys Met Phe Pro Ser Arg Cys Ser Gly Val Glu
100 105 110

His Phe Ile Leu Glu Val Ile Gly Arg Leu Pro Asp Met Glu Met Val
115 120 125

Ile Asn Val Arg Asp Tyr Pro Gln Val Pro Lys Trp Met Glu Pro Ala
130 135 140

Ile Pro Val Phe Ser Phe Ser Lys Thr Ser Glu Tyr His Asp Ile Met
145 150 155 160

Tyr Pro Ala Trp Thr Phe Trp Glu Gly Gly Pro Ala Val Trp Pro Ile
165 170 175

Tyr Pro Thr Gly Leu Gly Arg Trp Asp Leu Phe Arg Glu Asp Leu Val
180 185 190

Arg Ser Ala Ala Gln Trp Pro Trp Lys Lys Lys Asn Ser Thr Ala Tyr
195 200 205

Phe Arg Gly Ser Arg Thr Ser Pro Glu Arg Asp Pro Leu Ile Leu Leu
210 215 220

Ser Arg Lys Asn Pro Lys Leu Val Asp Ala Glu Tyr Thr Lys Asn Gln
225 230 235 240

Ala Trp Lys Ser Met Lys Asp Thr Leu Gly Lys Pro Ala Ala Lys Asp
245 250 255

Val His Leu Val Asp His Cys Lys Tyr Lys Tyr Leu Phe Asn Phe Arg
260 265 270

Gly Val Ala Ala Ser Phe Arg Phe Lys His Leu Phe Leu Cys Gly Ser
275 280 285

Leu Val Phe His Val Gly Asp Glu Trp Leu Glu Phe Phe Tyr Pro Gln
290 295 300

Leu Lys Pro Trp Val His Tyr Ile Pro Val Lys Thr Asp Leu Ser Asn
305 310 315 320

Val Gln Glu Leu Leu Gln Phe Val Lys Ala Asn Asp Asp Val Ala Gln
325 330 335

Glu Ile Ala Glu Arg Gly Ser Gln Phe Ile Arg Asn His Leu Gln Met
340 345 350

Asp Asp Ile Thr Cys Tyr Trp Glu Asn Leu Leu Ser Glu Tyr Ser Lys
355 360 365

Phe Leu Ser Tyr Asn Val Thr Arg Arg Lys Gly Tyr Asp Gln Ile Ile
370 375 380

Pro Lys Met Leu Lys Thr Glu Leu Xaa
385 390

<210> 155
<211> 75
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (75)
<223> Xaa equals stop translation

<400> 155
Met Leu Ile Leu Phe Leu Ser Val Cys Leu Phe Val Phe Leu Leu Thr
1 5 10 15

Val Arg Ala Leu Cys Cys Arg Ser Ala Gly Val Trp Leu Arg Ser Thr
20 25 30

Pro Asp Pro Val Cys Leu Gly Phe Ala Arg Gly Gly Cys Arg Ile Ala
35 40 45

Met Ile Ala Ala Cys Phe Ser Ser Gly Ser Phe Val Pro Glu Gly His
50 55 60

Pro Pro Asp Ala Ser Gln Ser Ser Pro Val Xaa
65 70 75

<210> 156
<211> 82
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (82)
<223> Xaa equals stop translation

<400> 156
Met Trp Pro Leu Leu Ala Val Ser Pro Phe Gly Leu Val Trp Ala Ser
1 5 10 15

Ser Gln Ser Gly Ser Leu Leu Leu Arg Ala Ser Ile Pro Arg Gln His
20 25 30

Ser Arg Arg Ala Trp His Phe Tyr Ser Glu Val Trp Gln Ser His Ser
35 40 45

Val Ala Ser Val Leu Leu Tyr Leu Leu Val Arg Ala Ile Thr Lys Met
50 55 60

Cys Ile Gly Ser Lys Lys Arg Asp Ile Thr Pro Thr Thr Arg Trp Lys
65 70 75 80

Lys Xaa

<210> 157
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (49)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (54)
<223> Xaa equals stop translation

<400> 157
Met Ser His His Ala Gly Leu Gly Gly Gly Ile Leu Phe Ser Leu Lys
1 5 10 15

Ile Ser Phe Phe Ile Ala Leu Ala Val Val Gly Gly Ser Arg Gly Val
20 25 30

Asn Asp Cys Gln Leu Gly Gly Cys Arg Val Gly Ser Cys Pro Arg Val
35 40 45

Xaa Val Arg Val Ala Xaa
50

<210> 158
<211> 103

<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (103)
<223> Xaa equals stop translation

<400> 158
Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
1 5 10 15

Trp Leu Leu Leu Lys Ala Gly Ala Val Arg Gly Ala Arg Ala Gly Pro
20 25 30

Arg Leu Pro Gly Arg Cys Cys Gly Ala Thr Cys Gly Asp Ala Gly Arg
35 40 45

Gly Trp Thr Phe Trp Ala Gln Pro Cys Pro Gln Lys Leu Leu Gly Gln
50 55 60

Lys Pro Gly Ala Gly Gly Cys Arg Gly Trp Val Leu Gly Trp Val Pro
65 70 75 80

Pro Arg Pro Glu Glu Pro Cys Ser Leu Ala Gly Lys Val Cys Thr Gly
85 90 95

Leu Ala Arg Trp Met Val Xaa
100

<210> 159
<211> 575
<212> PRT
<213> Homo sapiens

<400> 159
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr
35 40 45

Met Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser
50 55 60

Thr Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp
65 70 75 80

Leu Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly
85 90 95

Gln Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro
100 105 110

Ser Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly
        115   120   125

Pro Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser
    130   135   140

Ala Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala
145   150   155   160

Leu Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu
                165   170   175

Asp Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp
            180   185   190

Ala His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser
        195   200   205

Tyr Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly
    210   215   220

Ala Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys
225   230   235   240

His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser
                245   250   255

Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp
            260   265   270

Val Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His
        275   280   285

Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu
    290   295   300

Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn
305   310   315   320

Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro
                325   330   335

Trp Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg
            340   345   350

Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro
        355   360   365

Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg
    370   375   380

Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr
385   390   395   400

Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn
                405   410   415

Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro

420 425 430

Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr
435 440 445

Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe
450 455 460

Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln
465 470 475 480

Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val
485 490 495

Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr
500 505 510

Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg
515 520 525

Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr
530 535 540

Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His
545 550 555 560

Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
565 570 575

<210> 160
<211> 643
<212> PRT
<213> Homo sapiens

<400> 160
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
1 5 10 15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
20 25 30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
35 40 45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
50 55 60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
65 70 75 80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr
85 90 95

Leu Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His
100 105 110

Gly Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys

115 120 125

Thr Lys Ala Lys Leu Trp Leu Ala Lys Arg Gln Asn Pro Cys Leu Val
130 135 140

Thr Arg Ala Val Tyr Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu
145 150 155 160

Asn Arg Ser Ala Lys Asp Asn Gln Pro Val Leu Glu Ser Leu Gly Phe
165 170 175

Trp Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly
180 185 190

Phe Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser
195 200 205

Leu Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser
210 215 220

Gly Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu
225 230 235 240

Ser Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu
245 250 255

Lys Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro
260 265 270

Leu Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu
275 280 285

Asn His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met
290 295 300

Asp Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr
305 310 315 320

Pro Lys Glu Phe Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg
325 330 335

Ser Glu Ile Gln Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser
340 345 350

His His Met Gln Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu
355 360 365

Leu Lys Gln Trp Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu
370 375 380

Pro Thr Glu Ser Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr
385 390 395 400

Pro Leu Phe Leu Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr
405 410 415

Leu Ala Leu Trp Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln
420 425 430

```
Ala Val Arg Asp Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln
        435                 440                 445

Glu Asn Thr Cys Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala
    450                 455                 460

Ser Ile Ala Leu Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln
465                 470                 475                 480

Gln Trp Asp Gln Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu
                485                 490                 495

Leu Gly Glu Ser Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln
            500                 505                 510

Val Glu Glu Asp Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala
        515                 520                 525

Glu Thr Leu Ile Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu
    530                 535                 540

Leu Ser Lys Ser Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His
545                 550                 555                 560

Leu Gln Arg Met Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe
                565                 570                 575

Arg Glu Leu Pro Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr
            580                 585                 590

Arg Leu Arg Ile Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu
        595                 600                 605

Ala Phe Leu Glu Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val
    610                 615                 620

Trp Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu
625                 630                 635                 640

Ala Ala Cys


<210> 161
<211> 191
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (191)
<223> Xaa equals stop translation

<400> 161
Met Ser Ser Gly Thr Glu Leu Leu Trp Pro Gly Ala Ala Leu Leu Val
  1               5                  10                  15
```

```
Leu Leu Gly Val Ala Ala Ser Leu Cys Val Arg Cys Ser Arg Pro Gly
            20                  25                  30

Ala Lys Arg Ser Glu Lys Ile Tyr Gln Gln Arg Ser Leu Arg Glu Asp
        35                  40                  45

Gln Gln Ser Phe Thr Gly Ser Arg Thr Tyr Ser Leu Val Gly Gln Ala
    50                  55                  60

Trp Pro Gly Pro Leu Ala Asp Met Ala Pro Thr Arg Lys Asp Lys Leu
65                  70                  75                  80

Leu Gln Phe Tyr Pro Ser Leu Glu Asp Pro Ala Ser Ser Arg Tyr Gln
                85                  90                  95

Asn Phe Ser Lys Gly Ser Arg His Gly Ser Glu Glu Ala Tyr Ile Asp
            100                 105                 110

Pro Ile Ala Met Glu Tyr Tyr Asn Trp Gly Arg Phe Ser Lys Pro Pro
        115                 120                 125

Glu Asp Asp Asp Ala Asn Ser Tyr Glu Asn Val Leu Ile Cys Lys Gln
    130                 135                 140

Lys Thr Thr Glu Thr Gly Ala Gln Gln Glu Gly Ile Gly Gly Leu Cys
145                 150                 155                 160

Arg Gly Asp Leu Ser Leu Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser
                165                 170                 175

Gly Leu Cys Pro Ser Ala Ser Pro Glu Glu Asp Glu Gly Ile Xaa
            180                 185                 190


<210> 162
<211> 64
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (64)
<223> Xaa equals stop translation

<400> 162
Met Lys His Val Leu Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu
  1               5                  10                  15

Leu Ser Ile Phe Val Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu
            20                  25                  30

Ser Pro Ser Pro Gly Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn
        35                  40                  45

Thr Glu Pro Thr Lys Gly Leu Pro Asp His Pro Ser Arg Ser Met Xaa
    50                  55                  60
```

<210> 163
<211> 118
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (118)
<223> Xaa equals stop translation

<400> 163
```
Met Ile Phe Leu Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser
  1               5                  10                  15

Gly Phe Tyr His Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu
             20                  25                  30

Ala Leu Phe Phe Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln
         35                  40                  45

Leu Phe Cys Glu Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe
     50                  55                  60

Val Ser Leu Phe Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala
 65                  70                  75                  80

Gly Leu Phe Ile Val Leu Pro Ser Asp Val Phe Phe Ser Val His His
                 85                  90                  95

Leu Glu Ala Pro Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu
            100                 105                 110

Ile Ile Leu Leu Arg Xaa
        115
```

<210> 164
<211> 43
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals stop translation

<400> 164
```
Met Leu Leu Gln Phe Thr Leu Trp Val Phe Gly Ala Ile His Phe Pro
  1               5                  10                  15

Lys Cys Leu Gly Ile Lys Glu Glu Leu Leu Lys Cys Cys Leu Gln Leu
             20                  25                  30

Pro Pro Ser Ser Thr Tyr Glu Lys Val Val Xaa
         35                  40
```

<210> 165
<211> 48
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals stop translation

<400> 165
Met Leu Ser Arg Arg Leu His Cys Leu Val Leu Tyr Phe Leu Leu Leu
1 5 10 15

Leu Leu Ser Phe Ile His Thr Leu Ser Val Ser His Ile Cys Ser Ser
20 25 30

Phe Ile Trp Leu Phe Pro Lys Asn Ile Glu Ser Glu Ala Thr Met Xaa
35 40 45

<210> 166
<211> 46
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (46)
<223> Xaa equals stop translation

<400> 166
Met Glu Lys Met Gly Gln Gly Leu Leu Ser Ser Thr Tyr Leu Thr Val
1 5 10 15

Leu His Leu Ile Gln Leu Val Gly Cys Gly Leu Leu Thr Glu Glu Ile
20 25 30

Lys Glu Ser Lys Tyr Leu Ile Lys Thr Leu Gly Ser Gly Xaa
35 40 45

<210> 167
<211> 207
<212> PRT
<213> Homo sapiens

<400> 167
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Leu
35 40 45

Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys Phe
50 55 60

Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser Gly
65 70 75 80

Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys Leu Glu Gln Asp
85 90 95

Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln Gly Asn Leu Thr
100 105 110

Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys
115 120 125

Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu Ala Val Ala Ser
130 135 140

Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly Thr Gln Ser Ala
145 150 155 160

His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val Ser Asp Ser Ser
165 170 175

Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr Gln Ser Arg Gly
180 185 190

Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg Val Lys Asp
195 200 205

<210> 168
<211> 51
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (51)
<223> Xaa equals stop translation

<400> 168
Met Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val
1 5 10 15

Val Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro
20 25 30

Thr Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile
35 40 45

Val Gln Xaa
50

<210> 169
<211> 43
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals stop translation

<400> 169
```
Met Ala His Pro Gly Leu Pro Lys Thr Val Pro Val Tyr Ala Val Val
  1               5                  10                  15

Leu Ala Leu Leu Ile Met Thr Leu Pro Leu Thr Leu Thr Ile Asn Leu
             20                  25                  30

Asp Asp Asn Leu Tyr Gly Asn Ser Ala Lys Xaa
         35                  40
```

<210> 170
<211> 56
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (56)
<223> Xaa equals stop translation

<400> 170
```
Met Arg Pro Trp Trp Ser Leu Leu Leu Glu Ala Cys Ala Thr Cys Ala
  1               5                  10                  15

Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys Thr Gln Glu Val Ser His
             20                  25                  30

Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met Arg Arg Arg Cys Cys Leu
         35                  40                  45

Pro Ser Pro Arg Ser Cys Thr Xaa
     50                  55
```

<210> 171
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (109)
<223> Xaa equals stop translation

<400> 171
```
Met Ala Leu Ala Gly Ser Val Phe Val Leu Gly Gly Val Leu Val Leu
```

```
 1               5                  10                  15

Cys Val Glu Arg Asn Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu
             20                  25                  30

Pro Lys Ser Gln Pro Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser
        35                  40                  45

Phe Glu Arg Ser Trp Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met
    50                  55                  60

Val Thr Cys Arg Gln Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg
65                  70                  75                  80

Gly Gly Gly Pro Lys Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly
                85                  90                  95

Ala Cys Ala Val Arg Pro Glu Ile Gln Trp Glu Val Xaa
            100                 105


<210> 172
<211> 51
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals stop translation

<400> 172
Met Phe Leu Phe Phe Tyr Leu Ser Leu Ala Val Tyr Ala Gln Arg Gln
 1               5                  10                  15

Xaa Ser Gly Ser Cys Arg Gln Thr Asp His Arg Trp Lys Ser Arg Gly
            20                  25                  30

Ala Arg Arg Cys Phe Leu Glu Pro Arg Asp Pro Gly Ser Val Pro Gly
        35                  40                  45

His Pro Xaa
    50


<210> 173
<211> 566
<212> PRT
<213> Homo sapiens

<400> 173
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
 1               5                  10                  15
```

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Val Thr Trp Gly Leu Asn Arg Thr Leu Lys Pro Gln Arg Val Ile Val
50 55 60

Val Gly Ala Gly Val Ala Gly Leu Val Ala Ala Lys Val Leu Ser Asp
65 70 75 80

Ala Gly His Lys Val Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly
85 90 95

Arg Ile Phe Thr Tyr Arg Asp Gln Asn Thr Gly Trp Ile Gly Glu Leu
100 105 110

Gly Ala Met Arg Met Pro Ser Ser His Arg Ile Leu His Lys Leu Cys
115 120 125

Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn
130 135 140

Thr Trp Thr Glu Val His Glu Val Lys Leu Arg Asn Tyr Val Val Glu
145 150 155 160

Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly
165 170 175

His Ser Pro Glu Asp Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys
180 185 190

Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg
195 200 205

His Thr Leu Leu Glu Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro
210 215 220

Ala Val Gln Leu Leu Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr
225 230 235 240

Leu Ser Phe Ala Glu Ala Leu Arg Ala His Ser Cys Leu Ser Asp Arg
245 250 255

Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala
260 265 270

Leu Leu Ser Ser Leu Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val
275 280 285

Ala Met Thr Gln Gly Pro His Asp Val His Val Gln Ile Glu Thr Ser
290 295 300

Pro Pro Ala Arg Asn Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu
305 310 315 320

Thr Ala Ser Gly Pro Ala Val Lys Arg Ile Thr Phe Ser Pro Pro Leu
325 330 335

Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro Ala
340 345 350

Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu His
355 360 365

Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile Phe
370 375 380

Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr Trp
385 390 395 400

Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala Leu
405 410 415

Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val Arg
420 425 430

Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp Gln
435 440 445

His Ser Gln Gly Gly Phe Val Val Gln Pro Pro Ala Leu Trp Gln Thr
450 455 460

Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala Gly
465 470 475 480

Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys Leu
485 490 495

Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala Ser Asp
500 505 510

Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln Gly His
515 520 525

Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys Glu Glu
530 535 540

Gly Ser His Pro Pro Val Gln Gly Gln Leu Ser Leu Gln Asn Thr Thr
545 550 555 560

His Thr Arg Thr Ser His
565

<210> 174
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (76)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 174
Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro Pro Gly Arg
1   5   10   15

Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
            20   25   30

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
        35   40   45

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
    50   55   60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Xaa Leu Ala Glu Val
65   70   75   80

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
                85   90   95

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
            100   105   110

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
        115   120   125

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
    130   135   140

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
145   150   155   160

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
                165   170   175

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
            180   185   190

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
        195   200   205

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
    210   215   220

<210> 175
<211> 123
<212> PRT
<213> Homo sapiens

<400> 175
Met His Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys Pro Ser
1   5   10   15

Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Val His Leu Asn Ile

20 25 30

Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr
35 40 45

Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe Gln Tyr
50 55 60

Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly Leu Thr
65 70 75 80

Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe Asp Ser
85 90 95

Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg Ala Ala
100 105 110

Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
115 120

<210> 176
<211> 60
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (60)
<223> Xaa equals stop translation

<400> 176
Met Gly Leu Ser Val Leu Leu Pro Leu Cys Leu Leu Gly Pro Gly Arg
1 5 10 15

Phe Thr Ser Gly Gln Lys Pro Leu Asp Thr Pro Gly Leu Gly Ala Ala
20 25 30

Val Leu Ser Val Arg Lys Ala Gly Leu Lys Met Arg Ser His Leu Thr
35 40 45

Pro Ser Val Cys Thr Val Pro Ser Pro Gly Ser Xaa
50 55 60

<210> 177
<211> 105
<212> PRT
<213> Homo sapiens

<400> 177
Met Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg
1 5 10 15

Ile Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly
20 25 30

Gly Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr

35 40 45

Asn Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu
50 55 60

Val Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His
65 70 75 80

Ser His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe
85 90 95

Pro Cys His Glu Arg Lys Lys Gln Glu
100 105

<210> 178
<211> 88
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (88)
<223> Xaa equals stop translation

<400> 178
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
35 40 45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
50 55 60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
65 70 75 80

Ser Leu Leu Gly Pro Phe Ile Xaa
85

<210> 179
<211> 88
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (55)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (88)
<223> Xaa equals stop translation

<400> 179
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
35 40 45

Pro Val Glu Ala Pro Cys Xaa Glu Val Val Phe Lys Gln Lys Asn Gly
50 55 60

Lys Xaa Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
65 70 75 80

Ser Leu Leu Gly Pro Phe Ile Xaa
85

<210> 180
<211> 49
<212> PRT
<213> Homo sapiens

<400> 180
Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
35 40 45

Met

<210> 181
<211> 23
<212> PRT
<213> Homo sapiens

<400> 181
Leu Gly Ser Leu Ser Thr Ala Pro Ser Ser Ala Leu Pro Thr Leu Gly
1 5 10 15

Ala Arg Arg Thr Arg Ser Lys
20

<210> 182
<211> 104
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (104)
<223> Xaa equals stop translation

<400> 182
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
50 55 60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
65 70 75 80

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
85 90 95

Thr Arg Val Leu Phe Ile Tyr Xaa
100

<210> 183
<211> 198
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 183
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp

65 70 75 80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
180 185 190

Arg Val Leu Phe Ile Tyr
195

<210> 184
<211> 70
<212> PRT
<213> Homo sapiens

<400> 184
Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
1 5 10 15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
20 25 30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
35 40 45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
50 55 60

Arg Val Leu Phe Ile Tyr
65 70

<210> 185
<211> 82
<212> PRT
<213> Homo sapiens

<400> 185
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
50 55 60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
65 70 75 80

Leu Leu

<210> 186
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 186
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr
20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
35 40 45

<210> 187
<211> 34
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (34)
<223> Xaa equals stop translation

<400> 187
Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
20 25 30

Ser Xaa

<210> 188
<211> 232
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (232)
<223> Xaa equals stop translation

<400> 188
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
20 25 30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
35 40 45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
50 55 60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
65 70 75 80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
85 90 95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
100 105 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
115 120 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
130 135 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
145 150 155 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
165 170 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
180 185 190

Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
195 200 205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
210 215 220

Gly Phe Ile Leu Ile Pro Cys Xaa
225 230

<210> 189

<211> 457
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (457)
<223> Xaa equals stop translation

<400> 189
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
1 5 10 15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
20 25 30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
35 40 45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
50 55 60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
65 70 75 80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
85 90 95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
100 105 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
115 120 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
130 135 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145 150 155 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
165 170 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
180 185 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
195 200 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
210 215 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225 230 235 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
245 250 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
260 265 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
275 280 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
290 295 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305 310 315 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
325 330 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
340 345 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
355 360 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
370 375 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385 390 395 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
405 410 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
420 425 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
435 440 445

Cys Ser Asn Asp Cys Pro Arg Arg Xaa
450 455

<210> 190
<211> 185
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (185)
<223> Xaa equals stop translation

<400> 190
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg

35 40 45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
130 135 140

Thr Leu Lys Gly Asn Ser Trp Asn Cys Ser Arg Ser Pro His Leu Leu
145 150 155 160

Leu Tyr Thr Leu Val Arg Arg Gly Thr Asp Trp Ile Ser Tyr Phe Pro
165 170 175

Arg Gly Ser Gln Pro Asp Asn Gln Xaa
180 185

<210> 191
<211> 147
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (147)
<223> Xaa equals stop translation

<400> 191
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Leu Asp
50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp
85 90 95

```
Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
            100                 105                 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
        115                 120                 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
    130                 135                 140

Gly Leu Xaa
145


&lt;210&gt; 192
&lt;211&gt; 125
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (125)
&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 192
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
  1               5                  10                  15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
             20                  25                  30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
         35                  40                  45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
     50                  55                  60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
 65                  70                  75                  80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
                 85                  90                  95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
            100                 105                 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp Xaa
        115                 120                 125


&lt;210&gt; 193
&lt;211&gt; 52
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (52)
```

<223> Xaa equals stop translation

<400> 193
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
35 40 45

Leu Leu Ala Xaa
50

<210> 194
<211> 320
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (320)
<223> Xaa equals stop translation

<400> 194
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met
65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu

85 90 95

Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val
100 105 110

His Glu Xaa Lys Leu Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys
115 120 125

Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp
130 135 140

Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu
145 150 155 160

Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu
165 170 175

Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu
180 185 190

Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu
195 200 205

Ala Leu Arg Ala Xaa Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg
210 215 220

Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu
225 230 235 240

Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly
245 250 255

Pro His Asp Val His Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn
260 265 270

Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro
275 280 285

Ala Val Lys Arg Ile Thr Phe Ser Pro Arg Cys Pro Ala Thr Cys Arg
290 295 300

Arg Arg Cys Gly Gly Cys Thr Thr Cys Arg Pro Pro Arg Cys Ser Xaa
305 310 315 320

<210> 195
<211> 130
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 195
```
Pro Phe Cys Ser Gly Phe Phe Pro Ser Leu Trp Ile Tyr Leu Pro Phe
 1               5                  10                  15

Ile Phe Asn Val Ser Asp Leu Trp Met Gly Ser Leu Ser Gly Cys Ala
            20                  25                  30

Leu Pro Phe Cys Leu Xaa Val Phe Phe Leu Thr Val Ser Pro Ser Ala
        35                  40                  45

Val Gly Leu Leu Xaa Phe Ala Gly Gly Pro Leu Gln Thr Leu Phe Ala
    50                  55                  60

Trp Val Ser Pro Val Glu Ala Ala Glu Gln Gln Arg Leu Leu Pro Val
65                  70                  75                  80

Leu Ser Ser Gly Ser Phe Val Ser Glu Gly Thr Cys Gln Met Pro Ala
                85                  90                  95

Arg Ala Leu Leu Tyr Glu Val Ser Val Gly Pro Tyr Trp Glu Ile Pro
            100                 105                 110

Pro Ser Gln Asp Thr Arg Arg Ser Gly Thr Tyr Leu Arg Arg Gln Ser
        115                 120                 125

Asp Pro
    130
```

<210> 196
<211> 108
<212> PRT
<213> Homo sapiens

<400> 196
```
His Glu Gly Ser Cys Arg Ala Pro Gly Phe Ser Ala His Lys Gly Arg
 1               5                  10                  15

Gly Cys Pro Ser Pro Arg Met Thr Leu Pro Ser Arg Ala Leu Ala Ser
            20                  25                  30

Leu Gly Val Gly Val Trp Gly Met Leu Arg Leu Asn Gln Val Thr Val
        35                  40                  45

Ser Cys Gly Gly Ser Arg Trp Ser Ser Arg Val Ala Leu Gly Ala Phe
    50                  55                  60

Ser Trp Val Cys Gly Val Ala Leu Val Leu Gln Pro Ser Gly Gly Gly
65                  70                  75                  80

Leu Gly Leu Thr Ser Pro Ser Glu Gly Cys Trp Glu Gly Glu Leu Ala
                85                  90                  95
```

Leu Ala Val Leu Arg Ala Pro Gly Gly Ser Pro Ser
100 105

<210> 197
<211> 104
<212> PRT
<213> Homo sapiens

<400> 197
Ile Pro Leu Thr Leu Pro Gly Ile Phe Leu Leu Ile Arg Leu Phe Trp
1 5 10 15

Arg Leu Gly Gln Ser Ile Cys Gly Pro Gly Lys Leu Val Leu Trp Pro
20 25 30

Gln Phe Cys Cys Gly Cys Ala Val Ile Ser Gly His Cys Val Pro Arg
35 40 45

Gly Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu
50 55 60

Val Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser
65 70 75 80

Ala Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg
85 90 95

Gly Arg Gly Leu Ile Ser Gly Gly
100

<210> 198
<211> 237
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (142)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 198
Gly Pro Ala Gly Lys Glu Ala Trp Ile Trp Ser Trp Leu Leu Pro Ser
1 5 10 15

Pro Gly Pro Ala Pro Leu Pro Ser Ala Ser Trp Gly Leu Cys Gly Asp
20 25 30

Ala Pro Arg Ala Ala Ala Arg Gly Pro Val Glu Pro Gly Ala Ala Arg
35 40 45

Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Leu Met
50 55 60

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
65 70 75 80

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
85 90 95

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
100 105 110

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
115 120 125

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
130 135 140

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
145 150 155 160

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
165 170 175

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
180 185 190

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
195 200 205

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
210 215 220

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
225 230 235

<210> 199
<211> 8
<212> PRT
<213> Homo sapiens

<400> 199
Cys Cys Asn Gln His Asp Arg Cys
1 5

<210> 200
<211> 15
<212> PRT
<213> Homo sapiens

<400> 200
Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr
1 5 10 15

<210> 201
<211> 16
<212> PRT
<213> Homo sapiens

<400> 201
Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr Cys Gly

1 5 10 15

<210> 202
<211> 260
<212> PRT
<213> Homo sapiens

<400> 202
Gly Thr Ser Ser Ala Arg Pro Arg Gly Ala Leu Pro Gly Gly Ser Ala
1 5 10 15

Pro Ser Ala Pro His Gly Gln Leu Pro Gly Arg Ala Gln Pro Ala Pro
20 25 30

Val Ser Gly Pro Pro Pro Thr Ser Gly Leu Cys His Phe Asp Pro Ala
35 40 45

Ala Pro Trp Pro Leu Trp Pro Gly Pro Trp Gln Leu Pro Pro His Pro
50 55 60

Gln Asp Trp Pro Ala His Pro Asp Ile Pro Gln Asp Trp Val Ser Phe
65 70 75 80

Leu Arg Ser Phe Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr Val
85 90 95

Thr Gly Lys Trp Arg Gly Ser His Val Val Gly Leu Leu Thr Thr Leu
100 105 110

Asn Phe Gly Asp Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln Ala
115 120 125

Thr Val Leu Gly Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly Gln
130 135 140

Leu Val Leu Ile Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly Thr
145 150 155 160

Cys Leu Tyr Phe Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln Pro
165 170 175

Pro Ile Ser Cys Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser Pro
180 185 190

Arg Met Gly Glu Glu Cys Val Ser Val Trp Ser His Glu Gly Leu Val
195 200 205

Leu Thr Lys Leu Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser Arg
210 215 220

Leu Leu Val Leu Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu Cys
225 230 235 240

Cys Val Thr Ala Met Cys Phe His Pro Arg Arg Glu Ser His Trp Ser

245 250 255

Arg Thr Arg Leu
260

<210> 203
<211> 80
<212> PRT
<213> Homo sapiens

<400> 203
Ala Arg Ala Pro Pro Gly Pro Glu Gly Leu Ser Pro Glu Ala Gln Pro
1 5 10 15

Pro Leu Leu Pro Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu
20 25 30

Cys Leu Ala His His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu
35 40 45

Leu Leu Gly Leu Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His
50 55 60

Arg Thr Gly Leu Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe
65 70 75 80

<210> 204
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (143)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (186)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 204
Arg Phe Leu Ser Val Xaa Pro Gln Xaa Glu Val Pro Phe Leu Leu His
1 5 10 15

Pro Cys Val Cys Phe Xaa Gly Gly His Pro Ser Leu Leu Pro Asp Pro
20 25 30

Cys Arg Ala Val Gly Gly Gly Trp Glu Ala Pro Arg Cys Cys Leu His
35 40 45

Glu Ala Leu Cys Gln Ser Leu Gly Cys Lys Ala Glu Glu Ile Val Ser
50 55 60

Val Ser Glu Ser Ser Ser Ala Gln Arg Cys Trp Tyr Leu Leu Arg Gly
65 70 75 80

Arg Lys Ala Gly Gly Arg Gly Pro Ala Ser Pro Val Leu Phe Ala Leu
85 90 95

Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
100 105 110

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
115 120 125

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
130 135 140

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
145 150 155 160

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
165 170 175

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
180 185 190

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
195 200 205

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
210 215 220

<210> 205
<211> 199
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (103)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (191)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 205
Val Pro Gly Trp Pro Arg Ala Cys Ser Pro Cys Gln Ala Asp Ser Pro
1 5 10 15

Arg Ala His Pro Pro Lys Leu Arg Gly Ile Leu Arg Trp Ala Pro Val
20 25 30

Pro Leu Xaa Cys Ala Ala Leu Cys Pro Pro Leu Asp Ser Gly Met Ser
35 40 45

Met Ala Ala Cys Pro Glu Ala Pro Glu Pro Ser Phe Leu Arg Glu Val
50 55 60

Pro Ser Ser Pro Ala Ser Thr Gln Trp His Arg Pro Cys Asn Phe Arg
65 70 75 80

Gln Val Glu Ala Asn Pro Arg Lys Glu Pro Lys Asn Leu Val Trp Arg
85 90 95

Asp Val Ser Leu Gly Gln Xaa Ser Arg Thr Pro Arg Gly Ser Gly Leu
100 105 110

Glu Leu Val Arg Val Cys Gly Gly Gly Met Gln Arg Asp Lys Thr Val
115 120 125

Val Glu Glu Arg Val Gly Glu Glu Arg Glu Arg Glu Arg Glu Arg Glu
130 135 140

Ser Leu Gly Gly Ala Gly Lys His Gly Glu Met Arg Cys Val Tyr Val
145 150 155 160

Arg Glu Ser Val Gly Ala Pro Gly Arg Ala Gly Gly Gly Gly Asn Gly
165 170 175

Val Asn Ser Val Gly Cys Val Arg Thr Val His Ser Gly Ser Xaa Pro
180 185 190

Pro Pro Ser Ala Gly Val Ser
195

<210> 206
<211> 174
<212> PRT
<213> Homo sapiens

<400> 206
Thr Arg Pro Gly Lys Glu Leu Asn Leu Val Phe Gly Leu Gln Leu Ser
1 5 10 15

Met Ala Arg Ile Gly Ser Thr Val Asn Met Asn Leu Met Gly Trp Leu
20 25 30

Tyr Ser Lys Ile Glu Ala Leu Leu Gly Ser Ala Gly His Thr Thr Leu
35 40 45

Gly Ile Thr Leu Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile
50 55 60

Cys Ala Leu Ala Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu
65 70 75 80

His Lys Glu Gln Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val
85 90 95

Lys Asp Phe Ser Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys
100 105 110

Tyr Tyr Val Ala Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe
115 120 125

Thr Glu Lys Phe Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser
130 135 140

Val Val Tyr Val Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu
145 150 155 160

Val Asp Lys Thr Gly Lys Asn Ile Ile Trp Val Leu Cys Ala
165 170

<210> 207
<211> 31
<212> PRT
<213> Homo sapiens

<400> 207
Cys Lys Asp Leu Cys Ser Arg Val Tyr Leu Leu Thr Leu Ser Pro Leu
1 5 10 15

Leu Ser Tyr Asp Pro Ala Thr Ser His Ser Pro Arg Asn Thr Gln
20 25 30

<210> 208
<211> 369
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (78)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 208

```
Ile Ile Cys Glu Cys Trp Glu Glu Glu Cys Gln Ser Cys Arg Leu Lys
 1               5                  10                  15

Ile Thr Gln Pro Arg Glu Ile Cys Arg Met Asp Phe Leu Val Leu Phe
            20                  25                  30

Leu Phe Tyr Leu Ala Ser Val Leu Met Gly Leu Val Leu Ile Cys Val
        35                  40                  45

Cys Ser Lys Thr His Ser Leu Lys Gly Leu Ala Arg Gly Gly Ala Gln
    50                  55                  60

Ile Phe Ser Cys Ile Ile Pro Glu Cys Leu Gln Arg Ala Xaa His Gly
65                  70                  75                  80

Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe Ile Val Leu
                85                  90                  95

His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr Trp Glu Val
            100                 105                 110

Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr Leu Leu Leu
        115                 120                 125

Pro Tyr Leu Leu Leu Gly Val Asn Leu Phe Phe Phe Thr Leu Thr Cys
    130                 135                 140

Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu Leu Phe Leu
145                 150                 155                 160

His Val Tyr Glu Phe Asp Glu Val Met Phe Pro Lys Asn Val Arg Cys
                165                 170                 175

Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Lys His Cys Ser Val
            180                 185                 190

Cys Asn Trp Cys Val His Arg Phe Asp His His Cys Val Trp Val Asn
        195                 200                 205

Asn Cys Ile Gly Ala Trp Asn Ile Arg Tyr Phe Leu Ile Tyr Val Leu
    210                 215                 220

Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser Thr Thr Phe
225                 230                 235                 240

Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu Thr Tyr Ile
                245                 250                 255

Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe Leu Ile Gln
            260                 265                 270

Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu Gly Phe Val
        275                 280                 285

Val Val Leu Ser Phe Leu Leu Gly Gly Tyr Leu Leu Phe Val Leu Tyr
    290                 295                 300
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Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg Gly Asp Trp
305 310 315 320

Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro Ser Ala Glu
325 330 335

Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg Ser Asn Leu
340 345 350

Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg Lys Lys Gln
355 360 365

Glu

<210> 209
<211> 147
<212> PRT
<213> Homo sapiens

<400> 209
Leu Leu Ser Phe Lys Ile Arg Gly Leu Arg Thr Glu Asp Ala Gly Trp
1 5 10 15

Ala Gln Ser Ser Ser Gly Gly Leu Cys Val Arg Gly Asp Ala Phe Trp
20 25 30

Met Pro Ser Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
35 40 45

Ser Phe Leu Cys Leu Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
50 55 60

Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
65 70 75 80

Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
85 90 95

Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
100 105 110

Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
115 120 125

Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
130 135 140

Gly Gly Ile
145

<210> 210
<211> 143
<212> PRT
<213> Homo sapiens

<400> 210
Gln Leu Gly Leu Cys Leu Thr Ser Ala Ser Leu Pro Pro Ala Ser Arg
1 5 10 15

Cys Gly His Gln Ala Pro Leu Gly Ala Ser Asp Leu Ser Ala His His
20 25 30

Ser Ala Pro Gly Phe Ser Asp Ser Tyr Phe Thr Met Ser Cys Gln Ser
35 40 45

Ser Leu Ser Arg Ala Glu Ile Leu Gln Cys Pro Leu Val Pro Ser Val
50 55 60

Ser Pro Pro Thr His Leu Pro Gln Gly Arg Ala Asn Lys Ser Ser Arg
65 70 75 80

Ala Ser Leu Pro Leu Leu Pro Gln Thr His Trp Cys Leu Phe Pro Ser
85 90 95

Ala Arg Gly Trp Arg Arg Gly Ile Gln Ser Gly Leu Pro Pro Gly Gly
100 105 110

Ser Cys Thr Ser Pro Arg Ser Pro Pro Gln Thr Leu His Gln His Ile
115 120 125

Thr Leu Val Asn His Asn Thr Ser Tyr Trp Gln Ser Pro Ser Thr
130 135 140

<210> 211
<211> 160
<212> PRT
<213> Homo sapiens

<400> 211
His Gln Pro Pro Cys Leu Leu Pro Leu Ala Val Ala Thr Arg Pro Leu
1 5 10 15

Trp Gly His Leu Thr Cys Leu Pro Ile Ile Leu His Leu Val Ser Val
20 25 30

Thr Leu Thr Ser Pro Cys Leu Ala Asn Gln Ala Phe Gln Gly Gln Arg
35 40 45

Ser Tyr Asn Ala Leu Trp Cys Pro Leu Phe Leu Leu Leu Pro Thr Ser
50 55 60

Pro Lys Gly Glu Gln Thr Asn His Pro Glu Pro Ala Cys Pro Cys Phe
65 70 75 80

Pro Lys Leu Thr Gly Val Phe Ser Leu Gln His Val Val Gly Ala Glu
85 90 95

Glu Phe Ser Gln Val Phe Leu Leu Val Asp Pro Val Pro Val Leu Asp
100 105 110

His Leu Leu Lys Leu Phe Thr Ser Thr Ser His Leu Leu Ile Ile Ile
115 120 125

Pro His Ile Gly Lys Ala Pro Ala Pro Asp Ser Leu Leu Glu Glu Leu
    130   135   140

Ser Leu Ser Leu Ala Thr His Cys Lys Val Ala Val Ala Arg Phe Thr
145   150   155   160

<210> 212
<211> 157
<212> PRT
<213> Homo sapiens

<400> 212
Met Ala Ala Glu Gly Ser Arg Phe Ser Ser Gln Ser Pro Gly Leu Val
  1   5   10   15

Asp Arg Gln Gly Pro Lys Cys Asp Pro Ser Arg Leu Val Ser Pro Trp
             20   25   30

Gly Arg His Gly Leu Arg Ile Leu Gln Ile Gly His His His Gly Arg
         35   40   45

Asp Gly Gln His Glu Ala Thr His His Leu Leu Arg Val Leu Arg Ala
     50   55   60

Pro Arg Val Gly Lys Ala Asp Glu Gly Ala Val Asp Ser Asp Pro Ser
 65   70   75   80

Thr Pro Leu Gln Leu Lys His Glu Ala Ala His Ala Glu Asp His Ala
                 85   90   95

Gln Gln Val His Val Val Arg Arg Arg Val Val Gln Gly Arg Val Thr
            100   105   110

Phe Ala Arg Arg Gly Leu Val Pro Gln His Phe Val Arg Pro Pro Trp
        115   120   125

Val Arg His Ile Val Ser Gly His Ser Glu Ser Lys Ala Arg Ser Arg
    130   135   140

Leu Phe Arg Cys Arg Asn Arg Ser Phe Arg Arg Ala Ser
145   150   155

<210> 213
<211> 38
<212> PRT
<213> Homo sapiens

<400> 213
Arg Leu Val Ser Pro Trp Gly Arg His Gly Leu Arg Ile Leu Gln Ile
  1   5   10   15

Gly His His His Gly Arg Asp Gly Gln His Glu Ala Thr His His Leu

20 25 30

Leu Arg Val Leu Arg Ala
35

<210> 214
<211> 12
<212> PRT
<213> Homo sapiens

<400> 214
Pro Thr Asp Val Leu Lys Ile Arg Met Gln Ala Gln
1 5 10

<210> 215
<211> 7
<212> PRT
<213> Homo sapiens

<400> 215
Thr Tyr Glu Gln Leu Lys Arg
1 5

<210> 216
<211> 137
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (33)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (71)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 216
Arg Pro Arg Pro Ser Ala Ser Ser Leu Ala Arg Ser Ala Ser Leu Leu
1 5 10 15

Pro Ala Ala His Gly Xaa Gly Val Gly Gly Ala Gly Gly Gly Ser Ser
20 25 30

Xaa Leu Arg Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly
35 40 45

Glu Pro Glu Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile
50 55 60

Ser Ala Glu Ser Ala His Xaa Phe Asp Tyr Lys Asp Glu Ser Gly Phe
65 70 75 80

Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp
85 90 95

Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly
100 105 110

Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln
115 120 125

Leu Arg Ile Gly Asn Asp Gly Ile Phe
130 135

<210> 217
<211> 20
<212> PRT
<213> Homo sapiens

<400> 217
Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu Gln
1 5 10 15

Ala Ala Gly Asp
20

<210> 218
<211> 22
<212> PRT
<213> Homo sapiens

<400> 218
Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala
1 5 10 15

Asp Gln Leu Arg Ile Gly
20

<210> 219
<211> 103
<212> PRT
<213> Homo sapiens

<400> 219
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
50 55 60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
65 70 75 80

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
85 90 95

Thr Arg Val Leu Phe Ile Tyr
100

<210> 220
<211> 198
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 220
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp
65 70 75 80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr

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                                    150

          180                  185                  190

Arg Val Leu Phe Ile Tyr
        195


<210> 221
<211> 70
<212> PRT
<213> Homo sapiens

<400> 221
Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
  1               5                  10                  15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
             20                  25                  30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
         35                  40                  45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
     50                  55                  60

Arg Val Leu Phe Ile Tyr
 65                  70


<210> 222
<211> 82
<212> PRT
<213> Homo sapiens

<400> 222
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
  1               5                  10                  15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
             20                  25                  30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
         35                  40                  45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
     50                  55                  60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
 65                  70                  75                  80

Leu Leu


<210> 223
<211> 45
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 223
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr
20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
35 40 45

<210> 224
<211> 33
<212> PRT
<213> Homo sapiens

<400> 224
Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
20 25 30

Ser

<210> 225
<211> 189
<212> PRT
<213> Homo sapiens

<400> 225
Pro Arg Val Arg Ser Arg Glu Pro Val Ala Gly Ala Pro Gly Cys Gly
1 5 10 15

Thr Ala Gly Pro Pro Ala Met Ala Thr Leu Trp Gly Gly Leu Leu Arg
20 25 30

Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser Val Leu Leu
35 40 45

Leu Ala His Cys Gln Thr Pro Pro Ser Asp Cys Leu His Val Val Glu
50 55 60

Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys
65 70 75 80

Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val Thr Ile
85 90 95

Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr
100 105 110

```
Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly His Ala
        115                 120                 125

Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro Phe Ala
    130                 135                 140

Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn Val Leu
145                 150                 155                 160

Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val Gln Glu
                165                 170                 175

Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser
            180                 185


<210> 226
<211> 231
<212> PRT
<213> Homo sapiens

<400> 226
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
  1               5                  10                  15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
            20                  25                  30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
        35                  40                  45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
    50                  55                  60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
65                  70                  75                  80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
                85                  90                  95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
            100                 105                 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
        115                 120                 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
    130                 135                 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
145                 150                 155                 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
                165                 170                 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
            180                 185                 190
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Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
        195   200   205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
    210   215   220

Gly Phe Ile Leu Ile Pro Cys
225   230

<210> 227
<211> 456
<212> PRT
<213> Homo sapiens

<400> 227
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1   5   10   15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20   25   30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35   40   45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50   55   60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65   70   75   80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85   90   95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100   105   110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115   120   125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130   135   140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145   150   155   160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165   170   175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180   185   190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195   200   205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210   215   220

```
Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
                245                 250                 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385                 390                 395                 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
                405                 410                 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
            420                 425                 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
        435                 440                 445

Cys Ser Asn Asp Cys Pro Arg Arg
    450                 455


<210> 228
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (144)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<221> SITE
<222> (168)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 228
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Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu
 1               5                  10                  15

Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala
            20                  25                  30

Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu
        35                  40                  45

Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln
    50                  55                  60

Met Asn Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala
65                  70                  75                  80

Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly
                85                  90                  95

Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly
            100                 105                 110

His Ser Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg
        115                 120                 125

Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa
    130                 135                 140

Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg
145                 150                 155                 160

Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro
                165                 170                 175

Asn Ala Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr
            180                 185                 190

Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly
        195                 200                 205

Glu Cys Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala
    210                 215                 220

Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His
225                 230                 235                 240

Arg Ala Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn
                245                 250                 255

Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu
            260                 265                 270

Thr Leu Lys Ser Leu Gly Ala Leu Lys Lys
        275                 280
```

<210> 229
<211> 456
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (318)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (342)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 229
Val Ile Arg His Glu Gly Ser Thr Asn Met Glu Leu Ser Gln Met Ser
1 5 10 15

Xaa Leu Met Gly Leu Ser Val Leu Leu Gly Leu Leu Ala Leu Met Ala
20 25 30

Thr Ala Ala Val Xaa Arg Gly Trp Leu Arg Ala Gly Glu Glu Arg Ser
35 40 45

Gly Arg Pro Ala Cys Gln Lys Ala Asn Gly Phe Pro Pro Asp Lys Ser
50 55 60

Ser Gly Ser Lys Lys Gln Lys Gln Tyr Gln Arg Ile Arg Lys Glu Lys
65 70 75 80

Pro Gln Gln His Asn Phe Thr His Arg Leu Leu Ala Ala Ala Leu Lys
85 90 95

Ser His Ser Gly Asn Ile Ser Cys Met Asp Phe Ser Ser Asn Gly Lys
100 105 110

Tyr Leu Ala Thr Cys Ala Asp Asp Arg Thr Ile Arg Ile Trp Ser Thr
115 120 125

Lys Asp Phe Leu Gln Arg Glu His Arg Ser Met Arg Ala Asn Val Glu
130 135 140

Leu Asp His Ala Thr Leu Val Arg Phe Ser Pro Asp Cys Arg Ala Phe
145 150 155 160

Ile Val Trp Leu Ala Asn Gly Asp Thr Leu Arg Val Phe Lys Met Thr
165 170 175

Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu Asp Phe
180 185 190

Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala Asn Thr
195 200 205

Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu Ile Trp
210 215 220

Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln Met Asn
225 230 235 240

Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala Ser Cys
245 250 255

Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly Lys Lys
260 265 270

Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly His Ser
275 280 285

Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg Met Ala
290 295 300

Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa Val Glu
305 310 315 320

Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg Phe Glu
325 330 335

Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro Asn Ala
340 345 350

Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr Asn Thr
355 360 365

Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly Glu Cys
370 375 380

Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala Ser Cys
385 390 395 400

Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His Arg Ala
405 410 415

Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn Glu Ser
420 425 430

Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu Thr Leu
435 440 445

Lys Ser Leu Gly Ala Leu Lys Lys
450 455

<210> 230
<211> 363
<212> PRT
<213> Homo sapiens

<400> 230
Met Ser Val Met Val Val Arg Lys Lys Val Thr Arg Lys Trp Glu Lys
1 5 10 15

Leu Pro Gly Arg Asn Thr Phe Cys Cys Asp Gly Arg Val Met Met Ala
20 25 30

Arg Gln Lys Gly Ile Phe Tyr Leu Thr Leu Phe Leu Ile Leu Gly Thr
35 40 45

Cys Thr Leu Phe Phe Ala Phe Glu Cys Arg Tyr Leu Ala Val Gln Leu
50 55 60

Ser Pro Ala Ile Pro Val Phe Ala Ala Met Leu Phe Leu Phe Ser Met
65 70 75 80

Ala Thr Leu Leu Arg Thr Ser Phe Ser Asp Pro Gly Val Ile Pro Arg
85 90 95

Ala Leu Pro Asp Glu Ala Ala Phe Ile Glu Met Glu Ile Glu Ala Thr
100 105 110

Asn Gly Ala Val Pro Gln Gly Gln Arg Pro Pro Pro Arg Ile Lys Asn
115 120 125

Phe Gln Ile Asn Asn Gln Ile Val Lys Leu Lys Tyr Cys Tyr Thr Cys
130 135 140

Lys Ile Phe Arg Pro Pro Arg Ala Ser His Cys Ser Ile Cys Asp Asn
145 150 155 160

Cys Val Glu Arg Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val
165 170 175

Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr Leu Phe Ile Leu Ser Leu Ser
180 185 190

Leu Leu Thr Ile Tyr Val Phe Ala Phe Asn Ile Val Tyr Val Ala Leu
195 200 205

Lys Ser Leu Lys Ile Gly Phe Leu Glu Thr Leu Lys Glu Thr Pro Gly
210 215 220

Thr Val Leu Glu Val Leu Ile Cys Phe Phe Thr Leu Trp Ser Val Val
225 230 235 240

Gly Leu Thr Gly Phe His Thr Phe Leu Val Ala Leu Asn Gln Thr Thr
245 250 255

Asn Glu Asp Ile Lys Gly Ser Trp Thr Gly Lys Asn Arg Val Gln Asn
260 265 270

Pro Tyr Ser His Gly Asn Ile Val Lys Asn Cys Cys Glu Val Leu Cys

275 280 285

Gly Pro Leu Pro Pro Ser Val Leu Asp Arg Arg Gly Ile Leu Pro Leu
290 295 300

Glu Glu Ser Gly Ser Arg Pro Pro Ser Thr Gln Glu Thr Ser Ser Ser
305 310 315 320

Leu Leu Pro Gln Ser Pro Ala Pro Thr Glu Leu Asn Ser Asn Glu Met
325 330 335

Pro Glu Asp Ser Ser Thr Pro Glu Glu Met Pro Pro Pro Glu Pro Pro
340 345 350

Glu Pro Pro Gln Glu Ala Ala Glu Ala Glu Lys
355 360

<210> 231
<211> 184
<212> PRT
<213> Homo sapiens

<400> 231
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
35 40 45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
130 135 140

Thr Leu Lys Gly Asn Ser Trp Asn Cys Ser Arg Ser Pro His Leu Leu
145 150 155 160

Leu Tyr Thr Leu Val Arg Arg Gly Thr Asp Trp Ile Ser Tyr Phe Pro
165 170 175

Arg Gly Ser Gln Pro Asp Asn Gln

180

<210> 232
<211> 52
<212> PRT
<213> Homo sapiens

<400> 232
Leu His Glu Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr
1 5 10 15

Pro Trp Leu Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser
20 25 30

Pro Pro Trp Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro
35 40 45

Pro Cys Gly Leu
50

<210> 233
<211> 177
<212> PRT
<213> Homo sapiens

<400> 233
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Leu His Glu
115 120 125

Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr Pro Trp Leu
130 135 140

Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser Pro Pro Trp
145 150 155 160

Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro Pro Cys Gly
165 170 175

Leu

<210> 234
<211> 95
<212> PRT
<213> Homo sapiens

<400> 234
Pro Pro Val Pro Pro Trp Ile Ser Leu Pro Leu Thr Gly Ser Pro Pro
1 5 10 15

Arg Pro Gly Phe Val Pro Val Ser Pro Phe Cys Phe Ser Pro Met Thr
20 25 30

Asn Gly His Gln Val Leu Leu Leu Leu Leu Leu Thr Ser Ala Val Ala
35 40 45

Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp Met Cys
50 55 60

Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu Gly Gly
65 70 75 80

Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly Tyr
85 90 95

<210> 235
<211> 404
<212> PRT
<213> Homo sapiens

<400> 235
Ile Gln Gln Trp Gly Asp Ser Val Leu Gly Arg Arg Cys Arg Asp Leu
1 5 10 15

Leu Leu Gln Leu Tyr Leu Gln Arg Pro Glu Leu Arg Val Pro Val Pro
20 25 30

Glu Val Leu Leu His Ser Glu Gly Ala Ala Ser Ser Ser Val Cys Lys
35 40 45

Leu Asp Gly Leu Ile His Arg Phe Ile Thr Leu Leu Ala Asp Thr Ser
50 55 60

Asp Ser Arg Ala Leu Glu Asn Arg Gly Ala Asp Ala Ser Met Ala Cys
65 70 75 80

Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg His Leu Pro
85 90 95

Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn Phe Gln Glu
100 105 110

Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val Leu Gly Leu
115 120 125

Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His Gln Gly Ala
130 135 140

Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu Asn Tyr Arg
145 150 155 160

Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe Val Gln Phe
165 170 175

Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile Ser Phe Leu
180 185 190

Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp Asn Ser Asp
195 200 205

Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu Pro Ser Arg
210 215 220

Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu Glu Glu Ser
225 230 235 240

Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe Thr Pro Leu
245 250 255

Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser Arg Gly Gln
260 265 270

Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp Glu Met Ser
275 280 285

Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn Leu Gln Arg
290 295 300

Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala Phe Ser Leu
305 310 315 320

Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala Ala Phe Leu
325 330 335

Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu Val Val Gln
340 345 350

Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys Gln Glu His
355 360 365

Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met Tyr Gly Gln
370 375 380

Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile Leu His Met
385 390 395 400

Glu Ala Val Met

<210> 236
<211> 361
<212> PRT
<213> Homo sapiens

<400> 236
Met Leu Leu Lys His Leu Gln Arg Met Val Ser Val Pro Gln Val Lys
1 5 10 15

Ala Ser Ala Leu Lys Val Val Thr Leu Thr Ala Asn Asp Lys Thr Ser
20 25 30

Val Ser Phe Ser Ser Leu Pro Gly Gln Gly Val Ile Tyr Asn Val Ile
35 40 45

Val Trp Asp Pro Phe Leu Asn Thr Ser Ala Ala Tyr Ile Pro Ala His
50 55 60

Thr Tyr Ala Cys Ser Phe Glu Ala Gly Glu Gly Ser Cys Ala Ser Leu
65 70 75 80

Gly Arg Val Ser Ser Lys Val Phe Phe Thr Leu Phe Ala Leu Leu Gly
85 90 95

Phe Phe Ile Cys Phe Phe Gly His Arg Phe Trp Lys Thr Glu Leu Phe
100 105 110

Phe Ile Gly Phe Ile Ile Met Gly Phe Phe Phe Tyr Ile Leu Ile Thr
115 120 125

Arg Leu Thr Pro Ile Lys Tyr Asp Val Asn Leu Ile Leu Thr Ala Val
130 135 140

Thr Gly Ser Val Gly Gly Met Phe Leu Val Ala Val Trp Trp Arg Phe
145 150 155 160

Gly Ile Leu Ser Ile Cys Met Leu Cys Val Gly Leu Val Leu Gly Phe
165 170 175

Leu Ile Ser Ser Val Thr Phe Phe Thr Pro Leu Gly Asn Leu Lys Ile
180 185 190

Phe His Asp Asp Gly Val Phe Trp Val Thr Phe Ser Cys Ile Ala Ile
195 200 205

Leu Ile Pro Val Val Phe Met Gly Cys Leu Arg Ile Leu Asn Ile Leu
210 215 220

Thr Cys Gly Val Ile Gly Ser Tyr Ser Val Val Leu Ala Ile Asp Ser
225 230 235 240

Tyr Trp Ser Thr Ser Leu Ser Tyr Ile Thr Leu Asn Val Leu Lys Arg
245 250 255

Ala Leu Asn Lys Asp Phe His Arg Ala Phe Thr Asn Val Pro Phe Gln
260 265 270

Thr Asn Asp Phe Ile Ile Leu Ala Val Trp Gly Met Leu Ala Val Ser
275 280 285

Gly Ile Thr Leu Gln Ile Arg Arg Glu Arg Gly Arg Pro Phe Phe Pro
290 295 300

Pro His Pro Tyr Lys Leu Trp Lys Gln Glu Arg Glu Arg Arg Val Thr
305 310 315 320

Asn Ile Leu Asp Pro Ser Tyr His Ile Pro Pro Leu Arg Glu Arg Leu
325 330 335

Tyr Gly Arg Leu Thr Gln Ile Lys Gly Leu Phe Gln Lys Glu Gln Pro
340 345 350

Ala Gly Glu Arg Thr Pro Leu Leu Leu
355 360

<210> 237
<211> 116
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (40)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 237
Trp Ala Arg Leu Arg Gly Pro Gly Ala His Ala Arg Thr Ser Pro Gln
1 5 10 15

Pro Trp Arg Gly Pro Ser Pro Ala Gln Ala Ala Met Gly Phe Leu Gln
20 25 30

Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His Arg Val Ala Gly Ala
35 40 45

Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu Ile Glu Phe Ser Val
50 55 60

Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro Phe Pro Glu Glu Ala
65 70 75 80

Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe Leu Ile Phe Gln Ile
85 90 95

His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe Ser Pro Arg Arg Arg
100 105 110

Ser Pro Thr Met
115

<210> 238
<211> 166
<212> PRT
<213> Homo sapiens

<400> 238
Pro Arg Val Arg Pro Ala Ser Pro Pro Val Arg Ser Pro Ala Arg Trp
1 5 10 15

Gly Ser Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly
20 25 30

Val Gly Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro
35 40 45

Ala Leu Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala
50 55 60

Ser Pro Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln
65 70 75 80

Cys Pro Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala
85 90 95

Gly Ala Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala
100 105 110

Gln Arg Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala
115 120 125

Ser Gly Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr
130 135 140

Thr Pro Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro
145 150 155 160

Ala Leu Thr Leu Pro Pro
165

<210> 239
<211> 414
<212> PRT
<213> Homo sapiens

<400> 239
Pro Arg Val Arg Leu Ala Thr Pro Asn Ile Trp Asp Leu Ser Met Leu
1 5 10 15

Phe Ala Phe Ile Ser Leu Leu Val Met Leu Pro Thr Trp Trp Ile Val
20 25 30

Ser Ser Trp Leu Val Trp Gly Val Ile Leu Phe Val Tyr Leu Val Ile
35 40 45

Arg Ala Leu Arg Leu Trp Arg Thr Ala Lys Leu Gln Val Thr Leu Lys

50 55 60

Lys Tyr Ser Val His Leu Glu Asp Met Ala Thr Asn Ser Arg Ala Phe
65 70 75 80

Thr Asn Leu Val Arg Lys Ala Leu Arg Leu Ile Gln Glu Thr Glu Val
85 90 95

Ile Ser Arg Gly Phe Thr Leu Val Ser Ala Ala Cys Pro Phe Asn Lys
100 105 110

Ala Gly Gln His Pro Ser Gln His Leu Ile Gly Leu Arg Lys Ala Val
115 120 125

Tyr Arg Thr Leu Arg Ala Asn Phe Gln Ala Ala Arg Leu Ala Thr Leu
130 135 140

Tyr Met Leu Lys Asn Tyr Pro Leu Asn Ser Glu Ser Asp Asn Val Thr
145 150 155 160

Asn Tyr Ile Cys Val Val Pro Phe Lys Glu Leu Gly Leu Gly Leu Ser
165 170 175

Glu Glu Gln Ile Ser Glu Glu Glu Ala His Asn Phe Thr Asp Gly Phe
180 185 190

Ser Leu Pro Ala Leu Lys Val Leu Phe Gln Leu Trp Val Ala Gln Ser
195 200 205

Ser Glu Phe Phe Arg Arg Leu Ala Leu Leu Leu Ser Thr Ala Asn Ser
210 215 220

Pro Pro Gly Pro Leu Leu Thr Pro Ala Leu Leu Pro His Arg Ile Leu
225 230 235 240

Ser Asp Val Thr Gln Gly Leu Pro His Ala His Ser Ala Cys Leu Glu
245 250 255

Glu Leu Lys Arg Ser Tyr Glu Phe Tyr Arg Tyr Phe Glu Thr Gln His
260 265 270

Gln Ser Val Pro Gln Cys Leu Ser Lys Thr Gln Gln Lys Ser Arg Glu
275 280 285

Leu Asn Asn Val His Thr Ala Val Arg Ser Leu Gln Leu His Leu Lys
290 295 300

Ala Leu Leu Asn Glu Val Ile Ile Leu Glu Asp Glu Leu Glu Lys Leu
305 310 315 320

Val Cys Thr Lys Glu Thr Gln Glu Leu Val Ser Glu Ala Tyr Pro Ile
325 330 335

Leu Glu Gln Lys Leu Lys Leu Ile Gln Pro His Val Gln Ala Ser Asn
340 345 350

Asn Cys Trp Glu Glu Ala Ile Ser Gln Val Asp Lys Leu Leu Arg Arg
355 360 365

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Asn Thr Asp Lys Lys Gly Lys Pro Glu Ile Ala Cys Glu Asn Pro His
    370                 375                 380

Cys Thr Val Ser Thr Phe Glu Ala Ala Tyr Ser Thr His Cys Arg Gln
385                 390                 395                 400

Arg Ser Asn Pro Arg Gly Ala Gly Ile Arg Ser Leu Cys Arg
                405                 410


<210> 240
<211> 145
<212> PRT
<213> Homo sapiens

<400> 240
Ala Ala Pro His Pro Pro Leu Leu Arg Pro Leu Cys Leu Trp Cys Pro
  1               5                  10                  15

Leu Trp Pro Ala Trp Pro Leu Arg Gly Arg Pro Arg Ser Ala Trp Lys
            20                  25                  30

Arg Trp Pro Pro Leu Pro Val Gly Pro Ala Lys Leu Gly Cys Ser Met
        35                  40                  45

Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met Ser
    50                  55                  60

Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser Leu
 65                  70                  75                  80

Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp Asn
                 85                  90                  95

Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu Gly
            100                 105                 110

Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr Gln
        115                 120                 125

Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu Val
    130                 135                 140

Thr
145


<210> 241
<211> 72
<212> PRT
<213> Homo sapiens

<400> 241
Leu Gln Leu Ala Ser Gln Ser Ala Gly Ile Lys Gly Met Ser His Cys
  1               5                  10                  15

Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser Cys Phe Trp Ala
```

20 25 30

Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val Ser Phe Arg Pro
35 40 45

Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe Ile Leu Arg Ile
50 55 60

Leu Ile Leu Leu Arg Ser Phe Leu
65 70

<210> 242
<211> 140
<212> PRT
<213> Homo sapiens

<400> 242
Met Val Leu Val Leu Arg His Pro Leu Cys Ala Arg Glu Arg Ala Phe
1 5 10 15

Arg Glu Pro Gly Arg Gly Leu Leu Thr Arg Thr Gly Gln His Asp Gly
20 25 30

Ala Pro Ala Val Thr Ala Val Pro Gly Pro Leu Gly Ala Val Ala Ala
35 40 45

Ala Glu Gly Arg Arg Ser Ala Trp Gly Ala Gly Gly Ser Ser Pro Pro
50 55 60

Arg Lys Val Leu Trp Gly Asp Met Arg Gly Arg Arg Ala Gly Val Asp
65 70 75 80

Val Leu Gly Pro Ala Leu Ser Ser Glu Ala Ala Gly Ala Glu Ala Arg
85 90 95

Gly Trp Gly Met Pro Gly Met Gly Val Gly Val Gly Ala Ser Glu Thr
100 105 110

Arg Gly Ala Leu Phe Leu Gly Arg Glu Gly Val His Gly Pro Cys Pro
115 120 125

Met Asp Gly Leu Gly Pro Trp Pro Trp Gly Pro Trp
130 135 140

<210> 243
<211> 353
<212> PRT
<213> Homo sapiens

<400> 243
Met Gly Pro Ala Val Lys Met Trp Thr Asn Ala Trp Lys Gly Leu Asp
1 5 10 15

Asp Cys His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg
20 25 30

Cys Ser Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys
35 40 45

Leu Asp Val Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln
50 55 60

Cys His Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln
65 70 75 80

Thr Leu Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly
85 90 95

Gln Asn Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu
100 105 110

Arg Pro Trp Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser
115 120 125

Leu Arg Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys
130 135 140

Pro Pro Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu
145 150 155 160

Cys Arg Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly
165 170 175

Ser Tyr Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly
180 185 190

Lys Asn Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys
195 200 205

Gly Pro Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val
210 215 220

Asp Thr Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr
225 230 235 240

Cys Phe Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr
245 250 255

Leu Gln Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His
260 265 270

Asp Val Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn
275 280 285

Arg Thr Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala
290 295 300

Leu Arg Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala
305 310 315 320

Leu Thr Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro
325 330 335

Arg His Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro

340 345 350

Tyr

<210> 244
<211> 146
<212> PRT
<213> Homo sapiens

<400> 244
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Leu Asp
50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp
85 90 95

Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
100 105 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
115 120 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
130 135 140

Gly Leu
145

<210> 245
<211> 638
<212> PRT
<213> Homo sapiens

<400> 245
His Ala Ser Gly Ala Phe Leu Val Val Arg Gly Glu Pro Gln Gly Ser
1 5 10 15

Trp Gly Ser Met Thr Gly Val Ile Asn Gly Arg Lys Phe Gly Val Ala
20 25 30

Thr Leu Asn Thr Ser Val Met Gln Glu Ala His Ser Gly Val Ser Ser
35 40 45

Ile His Ser Ser Ile Arg His Val Pro Ala Asn Val Gly Pro Leu Met
50 55 60

Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala Arg
65 70 75 80

Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys Phe
85 90 95

Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr Met
100 105 110

Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser Thr
115 120 125

Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp Leu
130 135 140

Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly Gln
145 150 155 160

Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro Ser
165 170 175

Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly Pro
180 185 190

Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser Ala
195 200 205

Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala Leu
210 215 220

Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu Asp
225 230 235 240

Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp Ala
245 250 255

His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser Tyr
260 265 270

Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly Ala
275 280 285

Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys His
290 295 300

Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser Cys
305 310 315 320

Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp Val
325 330 335

Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His Asn
340 345 350

Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu Leu

355 360 365

Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn Val
370 375 380

Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro Trp
385 390 395 400

Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg Pro
405 410 415

Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro Gly
420 425 430

Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg Val
435 440 445

Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr Gln
450 455 460

Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn Cys
465 470 475 480

Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro Gly
485 490 495

Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr Pro
500 505 510

Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe Arg
515 520 525

Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln Tyr
530 535 540

Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val Ala
545 550 555 560

Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr Glu
565 570 575

Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg Pro
580 585 590

Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr Arg
595 600 605

Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His Gln
610 615 620

Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
625 630 635

<210> 246
<211> 367
<212> PRT
<213> Homo sapiens

<400> 246

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Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn His Pro Glu
 1               5                  10                  15

Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp Pro Gly Glu
            20                  25                  30

Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro Lys Glu Phe
        35                  40                  45

Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg Ser Glu Ile Gln
    50                  55                  60

Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser His His Met Gln
65                  70                  75                  80

Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu Leu Lys Gln Trp
                85                  90                  95

Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu Pro Thr Glu Ser
            100                 105                 110

Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr Pro Leu Phe Leu
        115                 120                 125

Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr Leu Ala Leu Trp
    130                 135                 140

Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln Ala Val Arg Asp
145                 150                 155                 160

Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln Glu Asn Thr Cys
                165                 170                 175

Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala Ser Ile Ala Leu
            180                 185                 190

Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln Gln Trp Asp Gln
        195                 200                 205

Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu Leu Gly Glu Ser
    210                 215                 220

Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln Val Glu Glu Asp
225                 230                 235                 240

Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala Glu Thr Leu Ile
                245                 250                 255

Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu Leu Ser Lys Ser
            260                 265                 270

Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His Leu Gln Arg Met
        275                 280                 285

Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe Arg Glu Leu Pro
    290                 295                 300
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Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr Arg Leu Arg Ile
305                 310                 315                 320

Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu Ala Phe Leu Glu
                325                 330                 335

Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val Trp Asp Ser Tyr
            340                 345                 350

Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala Ala Cys
        355                 360                 365


<210> 247
<211> 124
<212> PRT
<213> Homo sapiens

<400> 247
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
  1               5                  10                  15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
            20                  25                  30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
        35                  40                  45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
    50                  55                  60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
65                  70                  75                  80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
                85                  90                  95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
            100                 105                 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp
        115                 120


<210> 248
<211> 674
<212> PRT
<213> Homo sapiens

<400> 248
Met Thr Gly Arg Glu Phe Phe Ser Arg Phe Pro Glu Leu Tyr Pro Phe
  1               5                  10                  15

Leu Leu Lys Gln Leu Glu Thr Val Ala Asn Thr Val Asp Ser Asp Met
            20                  25                  30

Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val Leu
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        35                  40                  45

Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu Ser
    50                  55                  60

Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro Val
65                  70                  75                  80

Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val Met
                85                  90                  95

Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu Pro
            100                 105                 110

Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr Leu
        115                 120                 125

Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His Gly
    130                 135                 140

Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys Thr
145                 150                 155                 160

Lys Ala Lys Leu Trp Leu Ala Lys Arg Gln Asn Pro Cys Leu Val Thr
                165                 170                 175

Arg Ala Val Tyr Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu Asn
            180                 185                 190

Arg Ser Ala Lys Asp Asn Gln Pro Val Leu Glu Ser Leu Gly Phe Trp
        195                 200                 205

Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly Phe
    210                 215                 220

Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser Leu
225                 230                 235                 240

Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser Gly
                245                 250                 255

Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu Ser
            260                 265                 270

Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu Lys
        275                 280                 285

Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro Leu
    290                 295                 300

Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn
305                 310                 315                 320

His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp
                325                 330                 335

Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro
            340                 345                 350
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Lys Glu Phe Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg Ser
355 360 365

Glu Ile Gln Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser His
370 375 380

His Met Gln Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu Leu
385 390 395 400

Lys Gln Trp Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu Pro
405 410 415

Thr Glu Ser Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr Pro
420 425 430

Leu Phe Leu Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr Leu
435 440 445

Ala Leu Trp Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln Ala
450 455 460

Val Arg Asp Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln Glu
465 470 475 480

Asn Thr Cys Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala Ser
485 490 495

Ile Ala Leu Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln Gln
500 505 510

Trp Asp Gln Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu Leu
515 520 525

Gly Glu Ser Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln Val
530 535 540

Glu Glu Asp Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala Glu
545 550 555 560

Thr Leu Ile Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu Leu
565 570 575

Ser Lys Ser Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His Leu
580 585 590

Gln Arg Met Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe Arg
595 600 605

Glu Leu Pro Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr Arg
610 615 620

Leu Arg Ile Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu Ala
625 630 635 640

Phe Leu Glu Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val Trp
645 650 655

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Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala
            660                 665                 670

Ala Cys



<210> 249
<211> 10
<212> PRT
<213> Homo sapiens

<400> 249
Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly
  1               5                  10


<210> 250
<211> 230
<212> PRT
<213> Homo sapiens

<400> 250
Val Asp Gly Ile Asp Lys Leu Asp Ile Glu Phe Leu Gln Gln Phe Leu
  1               5                  10                  15

Glu Thr His Ser Arg Gly Pro Arg Leu His Ser Pro Gly His Ala Ser
             20                  25                  30

Gln Glu Ala Thr Pro Gly Ala Asn Met Ser Ser Gly Thr Glu Leu Leu
         35                  40                  45

Trp Pro Gly Ala Ala Leu Leu Val Leu Leu Gly Val Ala Ala Ser Leu
     50                  55                  60

Cys Val Arg Cys Ser Arg Pro Gly Ala Lys Arg Ser Glu Lys Ile Tyr
 65                  70                  75                  80

Gln Gln Arg Ser Leu Arg Glu Asp Gln Gln Ser Phe Thr Gly Ser Arg
                 85                  90                  95

Thr Tyr Ser Leu Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met
            100                 105                 110

Ala Pro Thr Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu Glu
        115                 120                 125

Asp Pro Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg His
    130                 135                 140

Gly Ser Glu Glu Ala Tyr Ile Asp Pro Ile Ala Met Glu Tyr Tyr Asn
145                 150                 155                 160

Trp Gly Arg Phe Ser Lys Pro Pro Glu Asp Asp Asp Ala Asn Ser Tyr
                165                 170                 175

Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly Ala Gln
            180                 185                 190
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Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp Leu Ser Leu Ser Leu
        195   200   205

Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys Pro Ser Ala Ser Pro
    210   215   220

Glu Glu Asp Glu Gly Ile
225   230

<210> 251
<211> 122
<212> PRT
<213> Homo sapiens

<400> 251
Val Leu Trp Arg Glu Ala Ser Ala Leu Val Leu Ser Asn Arg Leu Ser
  1   5   10   15

Ser Gly Leu Leu His Asp Leu Leu Leu Gln Pro Ala Ile His Ser Arg
             20   25   30

Leu Phe Pro Arg Arg Ser Arg Gly Leu Ser Glu Gly Glu Gly Ser Ser
         35   40   45

Val Ser Leu Gln Arg Ser Arg Val Leu Ser Ala Met Lys His Val Leu
     50   55   60

Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu Leu Ser Ile Phe Val
 65   70   75   80

Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu Ser Pro Ser Pro Gly
                 85   90   95

Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn Thr Glu Pro Thr Lys
            100   105   110

Gly Leu Pro Asp His Pro Ser Arg Ser Met
        115   120

<210> 252
<211> 129
<212> PRT
<213> Homo sapiens

<400> 252
Tyr Thr Phe His Thr Gln Ile Phe Leu Asp Phe Pro Met Ile Phe Leu
  1   5   10   15

Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser Gly Phe Tyr His
             20   25   30

Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu Ala Leu Phe Phe
         35   40   45

Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln Leu Phe Cys Glu

50 55 60

Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe Val Ser Leu Phe
65 70 75 80

Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala Gly Leu Phe Ile
85 90 95

Val Leu Pro Ser Asp Val Phe Phe Ser Val His His Leu Glu Ala Pro
100 105 110

Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu Ile Ile Leu Leu
115 120 125

Arg

<210> 253
<211> 99
<212> PRT
<213> Homo sapiens

<400> 253
Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
1 5 10 15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
20 25 30

Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
35 40 45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
50 55 60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
65 70 75 80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
85 90 95

Phe Phe Pro

<210> 254
<211> 51
<212> PRT
<213> Homo sapiens

<400> 254
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

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Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
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Leu Leu Ala
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<210> 255
<211> 259
<212> PRT
<213> Homo sapiens

<400> 255
Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
  1               5                  10                  15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
            20                  25                  30

Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
        35                  40                  45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
    50                  55                  60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
 65                  70                  75                  80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
                 85                  90                  95

Phe Phe Pro Leu Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe
            100                 105                 110

Asn Pro Lys Phe Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr
        115                 120                 125

Lys Lys Ser Gly Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys
    130                 135                 140

Leu Glu Gln Asp Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln
145                 150                 155                 160

Gly Asn Leu Thr Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys
                165                 170                 175

Pro Val Ser Cys Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu
            180                 185                 190

Ala Val Ala Ser Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly
        195                 200                 205

Thr Gln Ser Ala His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val
    210                 215                 220

Ser Asp Ser Ser Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr
225                 230                 235                 240
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Gln Ser Arg Gly Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg
245 250 255

Val Lys Asp

<210> 256
<211> 22
<212> PRT
<213> Homo sapiens

<400> 256
Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys Lys
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His Leu Ile Lys Ser His
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<210> 257
<211> 81
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 257
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His Phe Asn Xaa Ser Leu Arg Ser Phe Ser Phe Leu Arg Asn Gln Met
20 25 30

Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val Val
35 40 45

Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro Thr
50 55 60

Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile Val
65 70 75 80

Gln

<210> 258
<211> 77
<212> PRT
<213> Homo sapiens

<400> 258
Gly His Glu Ser Ile Cys Gly Ser Cys Arg Ser Trp Ile Tyr Phe Ser
1 5 10 15

Ile Arg Cys Arg Arg Arg Met Arg Pro Trp Trp Ser Leu Leu Leu Glu
20 25 30

Ala Cys Ala Thr Cys Ala Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys
35 40 45

Thr Gln Glu Val Ser His Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met
50 55 60

Arg Arg Arg Cys Cys Leu Pro Ser Pro Arg Ser Cys Thr
65 70 75

<210> 259
<211> 119
<212> PRT
<213> Homo sapiens

<400> 259
Lys Arg Ala Gly Val Glu Val Gly Gly Leu Val Met Ala Leu Ala Gly
1 5 10 15

Ser Val Phe Val Leu Gly Gly Val Leu Val Leu Cys Val Glu Arg Asn
20 25 30

Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu Pro Lys Ser Gln Pro
35 40 45

Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser Phe Glu Arg Ser Trp
50 55 60

Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met Val Thr Cys Arg Gln
65 70 75 80

Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg Gly Gly Gly Pro Lys
85 90 95

Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly Ala Cys Ala Val Arg
100 105 110

Pro Glu Ile Gln Trp Glu Val
115

<210> 260
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
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<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
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<223> Xaa equals any of the naturally occurring L-amino acids

<400> 260
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Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro Phe Glu Lys Cys Met
  1               5                  10                  15

Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val Thr Ile Leu Glu Ala
             20                  25                  30

Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr Arg Asp Gln Xaa Thr
         35                  40                  45

Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met Pro Ser Ser His Arg
     50                  55                  60

Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe
 65                  70                  75                  80

Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val His Glu Xaa Lys Leu
                 85                  90                  95

Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu
            100                 105                 110

Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp Ile Tyr Gln Met Ala
        115                 120                 125

Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala
    130                 135                 140

Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu Tyr Leu Leu Gly Glu
145                 150                 155                 160

Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu Gly Asp Val Met Ser
                165                 170                 175

Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu Ala Leu Arg Ala Xaa
            180                 185                 190

Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp
        195                 200                 205

Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu Ser Gly Leu Val Leu
    210                 215                 220

Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly Pro His Asp Val His
225                 230                 235                 240

Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn Leu Lys Val Leu Lys
                245                 250                 255

Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro Ala Val Lys Arg Ile
            260                 265                 270
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Thr Phe Ser
275

<210> 261
<211> 212
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (123)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 261
Leu Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro
1 5 10 15

Ala Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu
20 25 30

His Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile
35 40 45

Phe Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr
50 55 60

Trp Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala
65 70 75 80

Leu Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val
85 90 95

Arg Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp
100 105 110

Gln His Ser Gln Gly Gly Phe Val Val Gln Xaa Pro Ala Leu Trp Gln
115 120 125

Thr Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala
130 135 140

Gly Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys
145 150 155 160

Ser Ala Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala
165 170 175

Ser Asp Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln
180 185 190

Gly His Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys
195 200 205

Glu Glu Gly Ser
210

<210> 262
<211> 319
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 262
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met
65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu
85 90 95

Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val
100 105 110

His Glu Xaa Lys Leu Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys
115 120 125

Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp
130 135 140

Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu
145 150 155 160

Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu
165 170 175

Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu
180 185 190

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Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu
        195                 200                 205

Ala Leu Arg Ala Xaa Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg
    210                 215                 220

Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu
225                 230                 235                 240

Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly
                245                 250                 255

Pro His Asp Val His Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn
            260                 265                 270

Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro
        275                 280                 285

Ala Val Lys Arg Ile Thr Phe Ser Pro Arg Cys Pro Ala Thr Cys Arg
    290                 295                 300

Arg Arg Cys Gly Gly Cys Thr Thr Cys Arg Pro Pro Arg Cys Ser
305                 310                 315
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15849

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12N 15/11, 15/00, 15/63; C07H 21/02, 21/04
US CL : 536/23.1, 23.4; 435/320.1, 69.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.4; 435/320.1, 69.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Sequence searched SEQ ID NO:11, SEQ ID NO: 103, APS, STN, CAPLUS, terms nucleic acid, express, vector, pancreas islet cell tumors.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,849,498 A (BANDMAN et al) 15 December 1998, sequence listing.	1-10, 14-15, and 21
A	US 5,670,367 A (DORNER et al) 23 September 1997, especially sequence listing.	1-10, 14-15, and 21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 SEPTEMBER 1999	21 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. Lawrence Tai LI LEE Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15849

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 14-15, and 21

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15849

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-10, 14-15, and 21, drawn to isolated nucleic acid and expression system.
Group II, claim(s) 11-12 and 16, drawn to isolated polypeptide.
Group III, claim(s) 13, drawn to antibody.
Group IV, claim(s)17, drawn to method for preventing a medical condition.
Group V, claim(s) 18-19, drawn to method of diagnosing a disease.
Group VI, claim(s) 20, 22, drawn to method for identifying a binding partner.
Group VII, claim 23, drawn to product produced by method of claim 20.
This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is considered to be isolated nucleic acid and expression system.

The special technical feature of Group II is considered to be isolated polypeptide.

The special technical feature of Group III is considered to be antibody.

The special technical feature of Group IV is considered to be a method for preventing a medical condition..

The special technical feature of Group V is considered to be method of diagnosing a disease.

The special technical feature of Group VI is considered to be a method for identifying a binding partner..

The special technical feature of Group VII is considered to be product produced by method of claim 20.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

There are 71 genes, from gene Nos 1-71.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The 71 genes have different nucleic acid sequences and they are from different cell. Therefore they lack same special technical features.